(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 February 2014 (13.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/023691 A1

(51) International Patent Classification:
C07D 403/06 (2006.01) *A61K 31/513* (2006.01)
C07D 239/52 (2006.01) *A61P 31/12* (2006.01)
C07D 239/557 (2006.01) *A61P 31/14* (2006.01)
A61K 31/505 (2006.01) *A61P 31/16* (2006.01)
A61K 31/506 (2006.01) *A61P 31/20* (2006.01)

(21) International Application Number:
PCT/EP2013/066388

(22) International Filing Date:
5 August 2013 (05.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/679,968 6 August 2012 (06.08.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

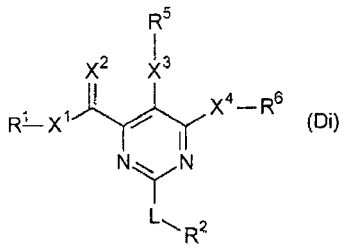
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: DIHYDROXYPYRIMIDINE CARBONIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT, AMELIORATION OR PREVENTION OF A VIRAL DISEASE



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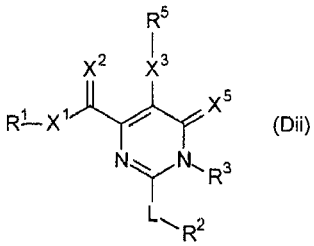

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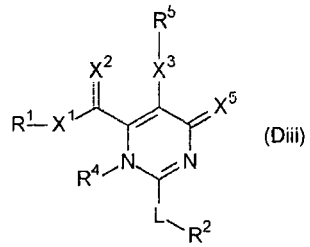

(Diii)

(57) Abstract: The present invention relates to a compound having the general formula (Di), (Dii), or (Diii), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, formula (Di), (Dii), (Diii) which are useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

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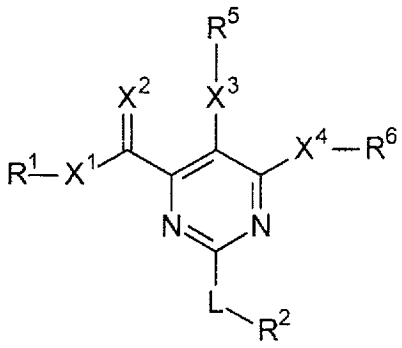
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Dihydroxypyrimidine carbonic acid derivatives and their use in the treatment, amelioration or prevention of a viral disease

Field of the invention

The present invention relates to a compound having the general formula (Di), (Dii), or (Diii), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



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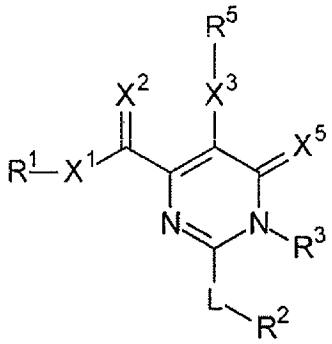

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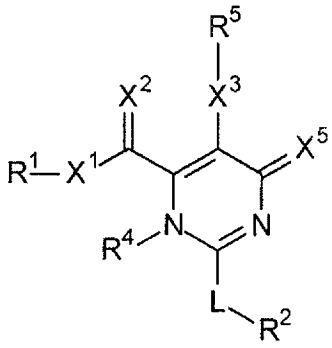


(Diii)

which is useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

Background of the invention

In recent years the serious threat posed by influenza virus to worldwide public health has been highlighted by, firstly, the ongoing low level transmission to humans of the highly pathogenic avian H5N1 strain (63% mortality in infected humans, http://www.who.int/

csr/disease/avian_influenza/en/) and secondly, the unexpected emergence in 2009 of a novel pandemic strain A/H1N1 that has rapidly spread around the entire world (http://www.who.int/csr/disease/swineflu/en/). Whilst the new strain is highly contagious but currently only generally gives mild illness, the future evolution of this virus is unpredictable. In a much more serious, but highly plausible scenario, H5N1 could have been more easily transmissible between humans or the new A/H1N1 could have been more virulent and could have carried the single point mutation that confers Tamiflu resistance (Neumann et al., Nature, 2009 (18; 459(7249) 931-939)); as many seasonal H1N1 strains have recently done (Dharan et al., The Journal of the American Medical Association, 2009 Mar 11; 301 (10), 1034-1041; Moscona et al., The New England Journal of Medicine, 2009 (Mar 5;360(10) pp 953-956)). In this case, the delay in generating and deploying a vaccine (~6 months in the relatively favourable case of A/H1N1 and still not a solved problem for H5N1) could have been catastrophically costly in human lives and societal disruption.

It is widely acknowledged that to bridge the period before a new vaccine becomes available and to treat severe cases, as well as to counter the problem of viral resistance, a wider choice of anti-influenza drugs is required. Development of new anti-influenza drugs has therefore again become a high priority, having been largely abandoned by the major pharmaceutical companies once the anti-neuraminidase drugs became available.

An excellent starting point for the development of antiviral medication is structural data of essential viral proteins. Thus, the crystal structure determination of e.g. the influenza virus surface antigen neuraminidase (Von Itzstein, M. et al., (1993), Nature, 363, pp. 418-423) led directly to the development of neuraminidase inhibitors with anti-viral activity preventing the release of virus from the cells, however, not the virus production. These and their derivatives have subsequently developed into the anti-influenza drugs, zanamivir (Glaxo) and oseltamivir (Roche), which are currently being stockpiled by many countries as a first line of defence against an eventual pandemic. However, these medicaments provide only a reduction in the duration of the clinical disease. Alternatively, other anti-influenza compounds such as amantadine and rimantadine target an ion channel protein, i.e., the M2 protein, in the viral membrane interfering with the uncoating of the virus inside the cell. However, they have not been extensively used due to their side effects and the rapid development of resistant virus mutants (Magden, J. et al., (2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621). In addition, more unspecific viral drugs, such as ribavirin, have been shown to work for treatment of influenza and other virus infections (Eriksson, B. et al., (1977), Antimicrob. Agents

Chemother., 11, pp. 946-951). However, ribavirin is only approved in a few countries, probably due to severe side effects (Furuta et al., ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2005, p. 981–986). Clearly, new antiviral compounds are needed, preferably directed against different targets.

Influenza virus as well as Thogotovirus belong to the family of Orthomyxoviridae which, as well as the family of the Bunyaviridae, including the Hantavirus, Nairovirus, Orthobunyavirus, and Phlebovirus, are negative stranded RNA viruses. Their genome is segmented and comes in ribonucleoprotein particles that include the RNA dependent RNA polymerase which carries out (i) the initial copying of the single-stranded virion RNA (vRNA) into viral mRNAs and (ii) the vRNA replication. This enzyme, a trimeric complex composed of subunits PA, PB1 and PB2, is central to the life cycle of the virus since it is responsible for the replication and transcription of viral RNA. In previous work the atomic structure of two key domains of the polymerase, the mRNA cap-binding domain in the PB2 subunit (Guilligay et al., Nature Structural & Molecular Biology 2008; May;15(5): 500-506) and the endonuclease-active site in the PA subunit (Dias et al., Nature 2009, 458, 914-918) have been identified and determined. These two sites are critical for the unique cap-snatching mode of transcription that is used by influenza virus to generate viral mRNAs. For the generation of viral mRNA the polymerase makes use of the so called "cap-snatching" mechanism (Plotch, S. J. et al., (1981), Cell, 23, pp. 847-858; Kukkonen, S. K. et al (2005), Arch. Virol., 150, pp. 533-556; Leahy, M. B. et al, (2005), J. Virol., 71, pp. 8347-8351; Noah, D. L. et al., (2005), Adv. Virus Res., 65, pp. 121-145). A 5' cap (also termed an RNA cap, RNA 7-methylguanosine cap or an RNA m7G cap) is a modified guanine nucleotide that has been added to the 5' end of a messenger RNA. The 5' cap consists of a terminal 7-methylguanosine residue which is linked through a 5'-5'-triphosphate bond to the first transcribed nucleotide. The viral polymerase binds to the 5' RNA cap of cellular mRNA molecules and cleaves the RNA cap together with a stretch of 10 to 15 nucleotides. The capped RNA fragments then serve as primers for the synthesis of viral mRNA.

The polymerase complex seems to be an appropriate antiviral drug target since it is essential for synthesis of viral mRNA and viral replication and contains several functional active sites likely to be significantly different from those found in host cell proteins (Magden, J. et al., (2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621). Thus, for example, there have been attempts to interfere with the assembly of polymerase subunits by a 25-amino-acid peptide resembling the PA-binding domain within PB1 (Ghanem, A. et al., (2007), J. Virol., 81, pp.

7801-7804). Furthermore, the endonuclease activity of the polymerase has been targeted and a series of 4-substituted 2,4-dioxobutanoic acid compounds has been identified as selective inhibitors of this activity in influenza viruses (Tomassini, J. et al., (1994), Antimicrob. Agents Chemother., 38, pp. 2827-2837). In addition, flutimide, a substituted 2,6-diketopiperazine, identified in extracts of Delitschia confertaspora, a fungal species, has been shown to inhibit the endonuclease of influenza virus (Tomassini, J. et al., (1996), Antimicrob. Agents Chemother., 40, pp. 1189-1193). Moreover, there have been attempts to interfere with viral transcription by nucleoside analogs, such as 2'-deoxy-2'-fluoroguanosine (Tisdale, M. et al., (1995), Antimicrob. Agents Chemother., 39, pp. 2454-2458).

Certain heterocyclic carboxamides which are stated to be useful in preventing or treating atherosclerosis or restenosis are disclosed in WO 2004/019933. The compounds are stated to be useful in these applications due to their activity against herpes viruses because atherosclerosis is related to a number of herpes virus infections.

WO 2011/046920 refers to DXR inhibitors which are stated to be suitable for antimicrobial therapy.

B. M. Baughman et al. identify influenza endonuclease inhibitors using a fluorescence polarization assay (*ACS Chem. Biol.* 2012, 7, 526–534).

It is an object of the present invention to identify further compounds which are effective against viral diseases and which have improved pharmacological properties.

Summary of the invention

Accordingly, in a first embodiment, the present invention provides a compound having the general formula (Di), (Dii), or (Diii).

It is understood that throughout the present specification the term "a compound having the general formula (Di), (Dii), or (Diii)" encompasses pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, codrugs, cocrystals, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

A further embodiment of the present invention relates to a pharmaceutical composition comprising a compound having the general formula (Di), (Dii), or (Diii) and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds having the general formula (Di), (Dii), or (Diii) are useful for treating, ameliorating or preventing viral diseases.

Detailed description of the invention

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. In the following passages different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference

in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Definitions

The term "alkyl" refers to a saturated straight or branched carbon chain.

The term "cycloalkyl" represents a cyclic version of "alkyl". The term "cycloalkyl" is also meant to include bicyclic, tricyclic and polycyclic versions thereof. Unless specified otherwise, the cycloalkyl group can have 3 to 12 carbon atoms.

The term "cyclic heteroalkyl" includes monocyclic, bicyclic, tricyclic and polycyclic heteroalkyl groups. Unless specified otherwise, the cyclic heteroalkyl group can have 3 to 12 atoms and can include one or more heteroatoms selected from N, O or S.

"Hal" or "halogen" represents F, Cl, Br and I.

The term "aryl" preferably refers to an aromatic monocyclic ring containing 6 carbon atoms, an aromatic bicyclic ring system containing 10 carbon atoms or an aromatic tricyclic ring system containing 14 carbon atoms. Examples are phenyl, naphthyl or anthracenyl, preferably phenyl.

The term "heteroaryl" preferably refers to a five-or six-membered aromatic ring wherein one or more of the carbon atoms in the ring have been replaced by 1, 2, 3, or 4 (for the five-membered ring) or 1, 2, 3, 4, or 5 (for the six-membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S. Examples of the heteroaryl group include pyrrole, pyrrolidine, oxolane, furan, imidazolidine, imidazole, pyrazole, oxazolidine, oxazole, thiazole, piperidine, pyridine, morpholine, piperazine, and dioxolane.

The term "hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring" refers to any group having 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and 2 as long as the group contains at least one ring. The term is also meant to include bicyclic, tricyclic and polycyclic versions thereof. If more than one ring is present, they can be separate

from each other or be annulated. The ring(s) can be either carbocyclic or heterocyclic and can be saturated, unsaturated or aromatic. The carbon atoms and heteroatoms can either all be present in the one or more rings or some of the carbon atoms and/or heteroatoms can be present outside of the ring, e.g., in a linker group (such as $-(CH_2)_p-$ with p = 1 to 6). Examples of these groups include –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl) wherein the aryl group can be, for example, phenyl, -(optionally substituted biphenyl), adamantyl, -(C_{3-7} cycloalkyl)-aryl as well as the corresponding compounds with a linker. Further examples of these groups include –(optionally substituted 3 to 7 membered cyclic heteroalkyl) or –(optionally substituted heteroaryl) containing, for instance, 1 to 3 N atoms.

The term "(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S)" refers to any mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S. This term includes monocyclic, bicyclic, tricyclic and polycyclic versions thereof. If more than one ring is present, they can be separate from each other or be annulated. The ring(s) can be either carbocyclic or heterocyclic and can be saturated, unsaturated or aromatic. The carbon atoms and heteroatoms can either all be present in the one or more rings or some of the carbon atoms and/or heteroatoms can be present outside of the ring, e.g., in a linker group (such as $-(CH_2)_p-$ with p = 1 to 6). Examples of these groups include –(optionally substituted C_{3-7} cycloalkyl), and –(optionally substituted aryl) wherein the aryl group can be, for example, phenyl or anthracenyl as well as the corresponding compounds with a linker.

If a compound or moiety is referred to as being "optionally substituted", it can in each instance include 1 or more of the indicated substituents, whereby the substituents can be the same or different.

The term "pharmaceutically acceptable salt" refers to a salt of a compound of the present invention. Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by mixing a solution of compounds of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine

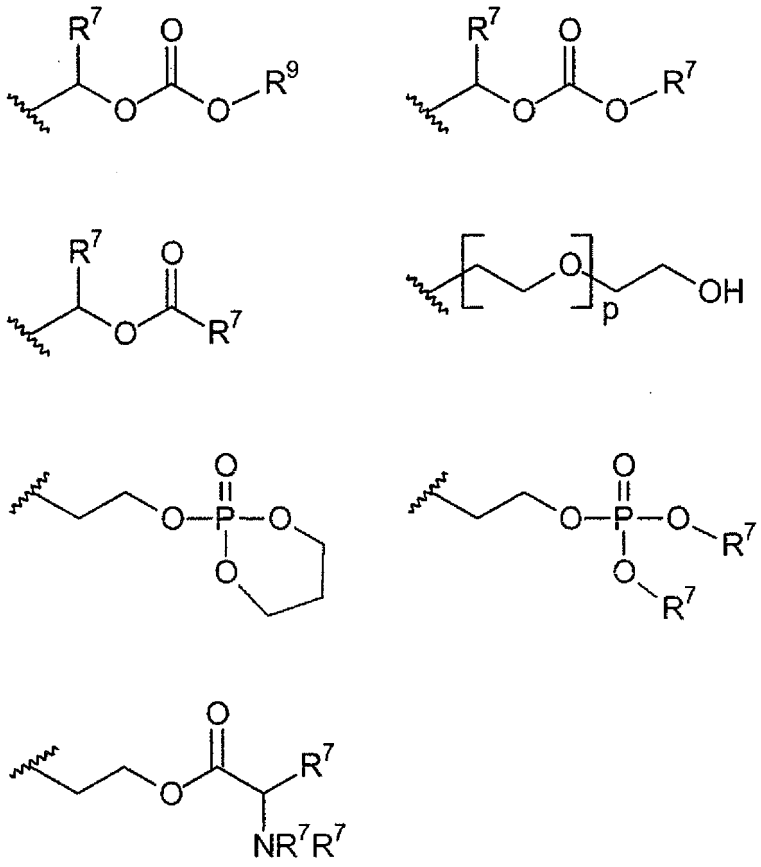
cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, S. M. Berge et al., "Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977)).

When the compounds of the present invention are provided in crystalline form, the structure can contain solvent molecules. The solvents are typically pharmaceutically acceptable solvents and include, among others, water (hydrates) or organic solvents. Examples of possible solvates include ethanolates and iso-propanolates.

The term "codrug" refers to two or more therapeutic compounds bonded via a covalent chemical bond. A detailed definition can be found, e.g., in N. Das et al., European Journal of Pharmaceutical Sciences, 41, 2010, 571--588.

The term "cocrystal" refers to a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric or non-stoichometric ratio of a target molecule or ion (i.e., compound of the present invention) and one or more neutral molecular cocrystal formers. A detailed discussion can be found, for example, in Ning Shan et al., Drug Discovery Today, 13(9/10), 2008, 440-446 and in D. J. Good et al., Cryst. Growth Des., 9(5), 2009, 2252–2264.

The compounds of the present invention can also be provided in the form of a prodrug, namely a compound which is metabolized *in vivo* to the active metabolite. Suitable prodrugs are, for instance, esters. Specific examples of suitable groups are given, among others, in US 2007/0072831 in paragraphs [0082] to [0118] under the headings prodrugs and protecting groups. If X^1 is O or S, preferred examples of the prodrug include compounds in which R^1 is replaced by one of the following groups:

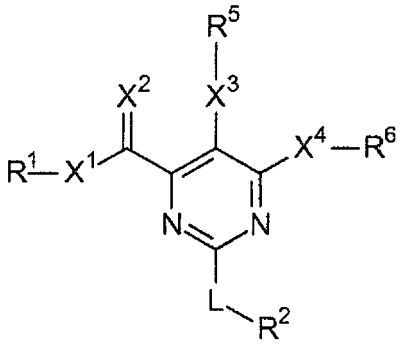


In these formulae, R^7 can be the same or different. R^9 is a cyclic group such as an aryl group or a C_{3-7} cycloalkyl group. p is 2 to 8.

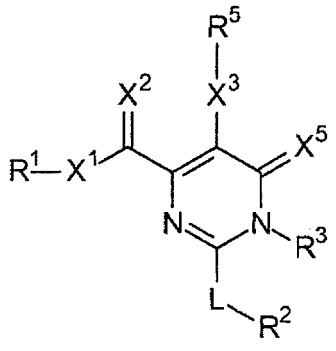
If X^1 is NR^*, preferred examples of the prodrug include compounds in which R^1 and R^* are not both H.

Compounds having the general formula (Di), (Dii), or (Diii)

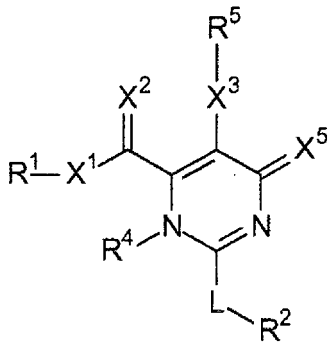
The present invention provides a compound having the general formula (Di), (Dii), or (Diii).



(Di)



(Dii)



(Diii)

The present invention provides a compound having the general formula (Di), (Dii), or (Diii) in which the following definitions apply.

X^1 is O, S or NR*; preferably O, or NR*.

X^2 is O or S; preferably O.

X^3 is O or S; preferably O.

X^4 is O or S; preferably O.

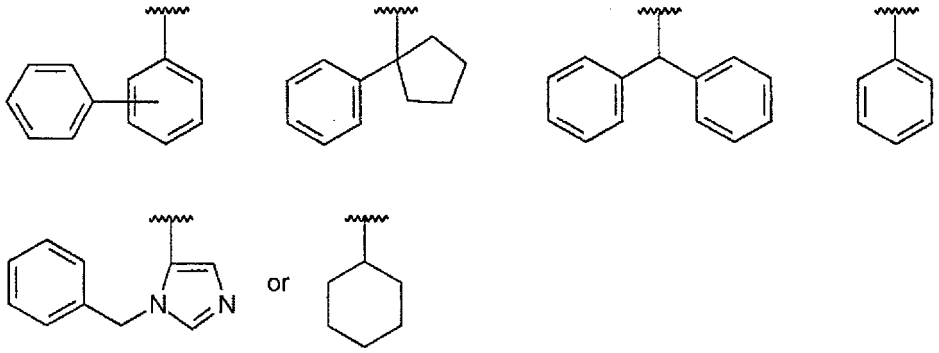
X^5 is O or S; preferably O.

L is $-(CH_2)_m-$, $-NR^*-SO_2-$ or $-SO_2-NR^*-$; preferably $-(CH_2)_m-$ or $-NR^*-SO_2-$.

m is 1 to 4; preferably m is 1 or 2; more preferably m is 1.

R^1 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted aryl), –C(O)–O–R** or $-P(O)(OR^{**})_2$. If X^1 is NR* then R^1 and R* can optionally be bound together to form a 5- to 7-membered ring. Preferably R^1 is –H or –(optionally substituted C_{1-6} alkyl).

R^2 is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring, wherein the hydrocarbon group can be optionally substituted. Preferably R^2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted C_{5-7} cycloalkyl, more preferably R^2 is selected from



wherein the heterocyclic group, phenyl group, cyclohexyl group or cyclopentyl group can be optionally substituted in any available position by a substituent which is independently selected from $-C_{1-6}$ alkyl, halogen, $-CF_3$, $-CN$, $-OH$, and $-O-C_{1-6}$ alkyl.

R^3 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or $-C_{1-4}$ alkyl–(optionally substituted aryl).

R^4 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or $-C_{1-4}$ alkyl–(optionally substituted aryl).

R^5 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl).

R^6 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl).

R^* is –H, or –(C_{1-6} alkyl); preferably –H.

R^{**} is –H, –(C_{1-6} alkyl), –(C_{3-7} cycloalkyl), –(aryl), or $-C_{1-4}$ alkyl–(aryl); preferably –(C_{1-6} alkyl) or –(aryl).

The optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, –NR*R*, –OH, and –O–C_{1-6} alkyl:

The optional substituent of the cycloalkyl group, the aryl group or the hydrocarbon group is selected from the group consisting of –C_{1-6} alkyl, –halogen, –CF_3, –CN, –X^1–R*, –aryl and –C_{1-4} alkyl–aryl.

The present inventors have surprisingly found that the compounds of the present invention which have a bulky, hydrophobic group represented by –L–R^2 have improved pharmacological properties compared to corresponding compounds which have a less space demanding group in this position. Without wishing to be bound by theory, it is assumed that the viral polymerase protein has a pocket for binding and that this hydrophobic group of the compounds of the present invention has improved binding compared to other groups. This could not have been predicted or expected based on the art.

The compounds of the present invention can be administered to a patient in the form of a pharmaceutical composition which can optionally comprise one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds of the present invention can be administered by various well known routes, including oral, rectal, intragastrical, intracranial and parenteral administration, e.g. intravenous, intramuscular, intranasal, intradermal, subcutaneous, and similar administration routes. Oral, intranasal and parenteral administration are particularly preferred. Depending on the route of administration different pharmaceutical formulations are required and some of those may require that protective coatings are applied to the drug formulation to prevent degradation of a compound of the invention in, for example, the digestive tract.

Thus, preferably, a compound of the invention is formulated as a syrup, an infusion or injection solution, a spray, a tablet, a capsule, a capslet, lozenge, a liposome, a suppository, a plaster, a band-aid, a retard capsule, a powder, or a slow release formulation. Preferably, the diluent is water, a buffer, a buffered salt solution or a salt solution and the carrier preferably is selected from the group consisting of cocoa butter and vitebesole.

Particular preferred pharmaceutical forms for the administration of a compound of the invention are forms suitable for injectionable use and include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the final solution or dispersion form must be sterile and fluid. Typically, such a solution or dispersion will include a solvent or dispersion medium, containing, for example, water-buffered aqueous solutions, e.g. biocompatible buffers, ethanol, polyol, such as glycerol, propylene glycol, polyethylene glycol, suitable mixtures thereof, surfactants or vegetable oils. A compound of the invention can also be formulated into liposomes, in particular for parenteral administration. Liposomes provide the advantage of increased half-life in the circulation, if compared to the free drug and a prolonged more even release of the enclosed drug.

Sterilization of infusion or injection solutions can be accomplished by any number of art recognized techniques including but not limited to addition of preservatives like anti-bacterial or anti-fungal agents, e.g. parabene, chlorobutanol, phenol, sorbic acid or thimersal. Further, isotonic agents, such as sugars or salts, in particular sodium chloride, may be incorporated in infusion or injection solutions.

Production of sterile injectable solutions containing one or several of the compounds of the invention is accomplished by incorporating the respective compound in the required amount in the appropriate solvent with various ingredients enumerated above as required followed by sterilization. To obtain a sterile powder the above solutions are vacuum-dried or freeze-dried as necessary. Preferred diluents of the present invention are water, physiological acceptable buffers, physiological acceptable buffer salt solutions or salt solutions. Preferred carriers are cocoa butter and vitebesole. Excipients which can be used with the various pharmaceutical forms of a compound of the invention can be chosen from the following non-limiting list:

a) binders such as lactose, mannitol, crystalline sorbitol, dibasic phosphates, calcium phosphates, sugars, microcrystalline cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone and the like;
b) lubricants such as magnesium stearate, talc, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,
c) disintegrants such as starches, croscarmellose, sodium methyl cellulose, agar, bentonite, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

In one embodiment the formulation is for oral administration and the formulation comprises one or more or all of the following ingredients: pregelatinized starch, talc, povidone K 30, croscarmellose sodium, sodium stearyl fumarate, gelatin, titanium dioxide, sorbitol, monosodium citrate, xanthan gum, titanium dioxide, flavoring, sodium benzoate and saccharin sodium.

If a compound of the invention is administered intranasally in a preferred embodiment, it may be administered in the form of a dry powder inhaler or an aerosol spray from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoro-alkane such as 1,1,1,2-tetrafluoroethane (HFA 134A™) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA™), carbon dioxide, or another suitable gas. The pressurized container, pump, spray or nebulizer may contain a solution or suspension of the compound of the invention, e.g., using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g., sorbitan trioleate.

Other suitable excipients can be found in the Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association, which is herein incorporated by reference.

It is to be understood that depending on the severity of the disorder and the particular type which is treatable with one of the compounds of the invention, as well as on the respective patient to be treated, e.g. the general health status of the patient, etc., different doses of the respective compound are required to elicit a therapeutic or prophylactic effect. The determination of the appropriate dose lies within the discretion of the attending physician. It is contemplated that the dosage of a compound of the invention in the therapeutic or prophylactic use of the invention should be in the range of about 0.1 mg to about 1 g of the active ingredient (i.e. compound of the invention) per kg body weight. However, in a preferred use of the present invention a compound of the invention is administered to a subject in need thereof in an amount ranging from 1.0 to 500 mg/kg body weight, preferably ranging from 1 to 200 mg/kg body weight. The duration of therapy with a compound of the invention will vary, depending on the severity of the disease being treated and the condition and idiosyncratic response of each individual patient. In one preferred embodiment of a prophylactic or therapeutic use, from 10 mg to 200 mg of the compound are orally administered to an adult

per day, depending on the severity of the disease and/or the degree of exposure to disease carriers.

As is known in the art, the pharmaceutically effective amount of a given composition will also depend on the administration route. In general, the required amount will be higher if the administration is through the gastrointestinal tract, e.g., by suppository, rectal, or by an intragastric probe, and lower if the route of administration is parenteral, e.g., intravenous. Typically, a compound of the invention will be administered in ranges of 50 mg to 1 g/kg body weight, preferably 10 mg to 500 mg/kg body weight, if rectal or intragastric administration is used and in ranges of 1 to 100 mg/kg body weight if parenteral administration is used. For intranasal administration, 1 to 100 mg/kg body weight are envisaged.

If a person is known to be at risk of developing a disease treatable with a compound of the invention, prophylactic administration of the biologically active blood serum or the pharmaceutical composition according to the invention may be possible. In these cases the respective compound of the invention is preferably administered in above outlined preferred and particular preferred doses on a daily basis. Preferably, from 0.1 mg to 1 g/kg body weight once a day, preferably 10 to 200 mg/kg body weight. This administration can be continued until the risk of developing the respective viral disorder has lessened. In most instances, however, a compound of the invention will be administered once a disease/disorder has been diagnosed. In these cases it is preferred that a first dose of a compound of the invention is administered one, two, three or four times daily.

The compounds of the present invention are particularly useful for treating, ameliorating, or preventing viral diseases. The type of viral disease is not particularly limited. Examples of possible viral diseases include, but are not limited to, viral diseases which are caused by Poxviridae, Herpesviridae, Adenoviridae, Papillomaviridae, Polyomaviridae, Parvoviridae, Hepadnaviridae, Retroviridae, Reoviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Hepeviridae, Caliciviridae, Astroviridae, Togaviridae, Flaviviridae, Deltavirus, Bornaviridae, and prions. Preferably viral diseases which are caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae, more preferably viral diseases which are caused by orthomyxoviridae.

Examples of the various viruses are given in the following table.

Family	Virus (preferred examples)
Poxviridae	Smallpox virus Molluscum contagiosum virus
Herpesviridae	Herpes simplex virus Varicella zoster virus Cytomegalovirus Epstein Barr virus Kaposi's sarcoma-associated herpesvirus
Adenoviridae	Human adenovirus A-F
Papillomaviridae	Papillomavirus
Polyomaviridae	BK-virus JC-Virsu
Parvoviridae	B19 virus Adeno associated virus 2/3/5
Hepadnaviridae	Hepatitis B virus
Retroviridae	Human immunodeficiency virus types 1/2 Human T-cell leukemia virus Human foamy virus
Reoviridae	Reovirus 1/2/3 Rotavirus A/B/C Colorado tick fever virus
Filoviridae	Ebola virus Marburg virus
Paramyxoviridae	Parainfluenza virus 1-4 Mumps virus Measles virus Respiratory syncytial virus Hendravirus
Rhabdoviridae	Vesicular stomatitis virus Rabies virus Mokola virus European bat virus Duvenhage virus
Orthomyxoviridae	Influenza virus types A-C
Bunyaviridae	California encephalitis virus La Crosse virus Hantaan virus Puumala virus Sin Nombre virus Seoul virus Crimean- Congo hemorrhagic fever virus

	Sakhalin virus Rift valley virus Sandfly fever virus Uukuniemi virus
Arenaviridae	Lassa virus Lymphocytic choriomeningitis virus Guanarito virus Junin virus, Machupo virus Sabia virus
Coronaviridae	Human coronavirus
Picornaviridae	Human enterovirus types A-D (Poliovirus, Echovirus, Coxsackie virus A/B) Rhinovirus types A/B/C Hepatitis A virus Parechovirus Food and mouth disease virus
Hepeviridae	Hepatitis E virus
Caliciviridae	Norwalk virus Sapporo virus
Astroviridae	Human astrovirus 1
Togaviridae	Ross River virus Chikungunya virus O'nyong-nyong virus Rubella virus
Flaviviridae	Tick-borne encephalitis virus Dengue virus Yellow Fever virus Japanese encephalitis virus Murray Valley virus St. Louis encephalitis virus West Nile virus Hepatitis C virus Hepatitis G virus Hepatitis GB virus
Deltavirus	Hepatitis deltavirus
Bornaviridae	Bornavirus
Prions	

Preferably, the compounds of the present invention are employed to treat influenza. Within the present invention, the term "influenza" includes influenza A, B, C, isavirus and thogotovirus and also covers bird flu and swine flu. The subject to be treated is not particularly restricted and can be any vertebrate, such as birds and mammals (including humans).

Without wishing to be bound by theory it is assumed that the compounds of the present invention are capable of inhibiting endonuclease activity, particularly of the influenza virus. More specifically it is assumed that they directly interfere with the N-terminal part of the influenza PA protein, which harbours endonuclease activity. However, delivery of a compound into a cell may represent a problem depending on, e.g., the solubility of the compound or its capabilities to cross the cell membrane. The present invention not only shows that the claimed compounds have *in vitro* polymerase inhibitory activity but also *in vivo* antiviral activity.

A possible measure of the *in vitro* polymerase inhibitory activity of the compounds having the formula (Di), (Dii), (Diii), (A) and/or (C) is the FRET endonuclease activity assay disclosed herein. Preferably, the compounds exhibit a % reduction of at least about 50 % at 25 µM in the FRET assay. In this context, the % reduction is the % reduction of the initial reaction velocity (v0) of substrate cleavage of compound-treated samples compared to untreated samples. Preferably, the compounds exhibit an IC_{50} of at least about 40 µM, more preferably at least about 20 µM, in the FRET assay. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the initial reaction velocities (v0) in a given concentration series ranging from maximum 100 µM to at least 2 nM.

A possible measure of the *in vivo* antiviral activity of the compounds having the formula (Di), (Dii), (Diii), (A) and/or (C) is the CPE assay disclosed herein. Preferably, the compounds exhibit a % reduction of at least about 30 % at 50 µM. In this connection, the reduction in the virus-mediated cytopathic effect (CPE) upon treatment with the compounds was calculated as follows: The cell viability of infected-treated and uninfected-treated cells was determined using an ATP-based cell viability assay (Promega). The response in relative luminescent units (RLU) of infected-untreated samples was subtracted from the response (RLU) of the infected-treated samples and then normalized to the viability of the corresponding uninfected sample resulting in % CPE reduction. Preferably, the compounds exhibit an IC_{50} of at least about 45 µM, more preferably at least about 10 µM, in the CPE assay. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the RLU response in a given concentration series ranging from maximum 100 µM to at least 100 nM.

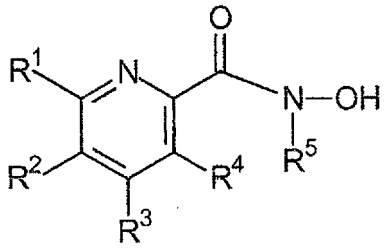
The compounds having the general formula (Di), (Dii), or (Diii) can be used in combination with one or more other medicaments. The type of the other medicaments is not particularly

limited and will depend on the disorder to be treated. Preferably, the other medicament will be a further medicament which is useful in treating, ameloriating or preventing a viral disease, more preferably a further medicament which is useful in treating, ameloriating or preventing influenza.

The following combinations of medicaments are envisaged as being particularly suitable:

(i) The combination of endonuclease and cap-binding inhibitors (particularly targeting influenza). The endonuclease inhibitors are not particularly limited and can be any endonuclease inhibitor, particularly any viral endonuclease inhibitor. Preferred endonuclease inhibitors are those having the general formula (I) as defined in the US application with the serial number 61/550,045, filed on October 21, 2011, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of the compounds according to US 61/550,045, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference.

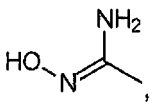
The compounds having the general formula (I) of this reference can optionally be in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof. They are defined as follows (wherein the definitions of the various moieties given in this earlier application apply):



(I)

wherein

R^1 is selected from –H, $-C_{1-6}$ alkyl, $-(C_{3-7}$ cycloalkyl) and $-CH_2-(C_{3-7}$ cycloalkyl);

R^2 is selected from –H,  , $-C_{1-6}$ alkyl, –Hal, $-(C_{3-7}$ cycloalkyl), $-CH_2-(C_{3-7}$ cycloalkyl), $-(CH_2)_m-$(optionally substituted aryl), –(optionally substituted 5- or 6-

membered heterocyclic ring which contains at least one heteroatom selected from N, O and S, wherein the substituent is selected from $-C_{1-4}$ alkyl, –halogen, –CN, $-CHal_3$, –aryl, $-NR^6R^7$, and $-CONR^6R^7$;

R^3 is selected from –H, $-C_{1-6}$ alkyl,
$-(CH_2)_n-NR^6R^8$,
–(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, $-C_{1-4}$ alkyl, $-NR^9R^{10}$, $-(CH_2)_n-OH$, $-C(O)-NR^9R^{10}$, $-SO_2-NR^9R^{10}$, $-NH-C(O)-O-R^{11}$, $-C(O)-O-R^{11}$, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S;

or wherein R^1 and R^2 together form a phenyl ring or wherein R^2 and R^3 together form a phenyl ring;

R^4 is –H;

R^5 is selected from the group consisting of –H or $-(CH_2)_n-$(optionally substituted aryl), wherein the substituent is selected from –Hal and $-C_{1-4}$ alkyl; or wherein R^4 and R^5 together form a methylene group $-CH_2-$, ethylene group $-CH_2CH_2-$ or ethyne group –CHCH–, which can be optionally substituted by $-C_{1-4}$ alkyl, –halogen, $-CHal_3$, $-R^6R^7$, $-OR^6$, $-CONR^6R^7$, $-SO_2R^6R^7$, aryl or heteroaryl;

R^6 is selected from –H and $-C_{1-4}$ alkyl;

R^7 is selected from –H and $-C_{1-4}$ alkyl;

R^8 is selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_n-$(optionally substituted aryl), $-SO_2-(CH_2)_n-$(optionally substituted aryl), $-SO_2-(CH_2)_n-$(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), $-(CH_2)_n-$(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, $-CF_3$, $-C_{1-4}$ alkyl, and $-(CH_2)_n-$aryl;

R^9 is selected from –H, $-C_{1-4}$ alkyl, and $-C_{1-4}$ alkylene$-NR^{11}R^{11}$;

R^{10} is selected from –H, $–C_{1–4}$ alkyl, and $–C_{1–4}$ alkylene–$NR^{11}R^{11}$;

R^{11} is selected from –H, $–CF_3$, and $–C_{1–4}$ alkyl;

each **m** is 0 or 1; and

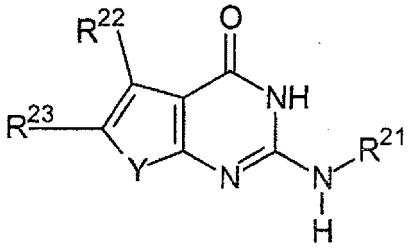
each **n** is independently 0, 1, 2, or 3.

Further preferred endonuclease inhibitors are those having the general formula (A) as defined in the copending application with attorney's docket number T3448 US, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of the compounds having the general formula (A), the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference. The compounds having the general formula (A) can be optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof. They are defined below.

Further preferred endonuclease inhibitors are those having the general formula (C) as defined in the copending application with attorney's docket number T3450 US, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of the compounds having the general formula (C), the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference. The compounds having the general formula (C) can be optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof. They are defined below.

The cap-binding inhibitors are not particularly limited either and can be any cap-binding inhibitor, particularly any viral cap-binding inhibitor. Preferred cap-binding inhibitors are those having the general formula (II) as defined in US application 61/550,057 and/or the compounds disclosed in WO2011/000566, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of the compounds according to US 61/550,057 or WO2011/000566, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference.

The compound having the general formula (II) can be optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof. It is defined as follows:



(II)

wherein

Y is S;

$\mathbf{R^{21}}$ is selected from –H, $-C_{1-6}$alkyl, $-(CH_2)_q$–aryl, $-(CH_2)_q$–heterocyclyl, $-(CH_2)_q$–cycloalkyl, $-(CH_2)_p-OR^{25}$, and $-(CH_2)_p-NR^{25}R^{26}$;

$\mathbf{R^{22}}$ is selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_q$–cycloalkyl, –Hal, $-CF_3$ and –CN;

$\mathbf{R^{23}}$ is selected from –aryl, –heterocyclyl, –cycloalkyl, $-C(-R^{28})(-R^{29})$–aryl, $-C(-R^{28})(-R^{29})$–heterocyclyl, and $-C(-R^{28})(-R^{29})$–cycloalkyl;

$\mathbf{R^{25}}$ is selected from –H, $-C_{1-6}$ alkyl, and $-(CH_2CH_2O)_rH$;

$\mathbf{R^{26}}$ is selected from –H, and $-C_{1-6}$ alkyl;

R^{27} is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, -Hal, $-CF_3$, -CN, $-COOR^{25}$, $-OR^{25}$, $-(CH_2)_qNR^{25}R^{26}$, $-C(O)-NR^{25}R^{26}$, and $-NR^{25}-C(O)-C_{1-6}$ alkyl;

R^{28} and R^{29} are independently selected from -H, $-C_{1-6}$ alkyl, $-(CH_2)_q$-aryl, $-(CH_2)_q$-heterocyclyl, $-(CH_2)_q$-cycloalkyl, -OH, $-O-C_{1-6}$ alkyl, $-O-(CH_2)_q$-aryl, $-O-(CH_2)_q$-heterocyclyl, and $-O-(CH_2)_q$-cycloalkyl;

or R^{28} and R^{29} are together =O, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$;

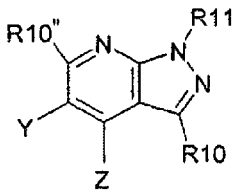
p is 1 to 4;

q is 0 to 4; and

r is 1 to 3;

wherein the aryl group, heterocyclyl group and/or cycloalkyl group can be optionally substituted with one or more substituents R^{27}.

The compounds of WO2011/000566 have the general formula (XXI):



(XXI)

or a pharmaceutically effective salt, a solvate, a prodrug, a tautomer, a racemate, an enantiomer or a diastereomer thereof;

wherein

one of **Y** and **Z** is $-XR^{12}$ and the other is $R^{10'}$;

R^{10}, $R^{10'}$ and $R^{10''}$ are each individually selected from the group consisting of hydrogen, C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2-C_8-alkynyl, $-(CH_2)_nC(O)OH$, $-(CH_2)_nC(O)OR^{16}$, $-(CH_2)_nOH$, $-(CH_2)_nOR^{16}$, $-CF_3$, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_nC(O)NH_2$, $-(CH_2)_nC(O)NHR^{16}$, $-(CH_2)_nC(O)NR^{16}R^{17}$, $-(CH_2)_nS(O)_2NH_2$, $-(CH_2)_nS(O)_2NHR^{16}$, $-(CH_2)_nS(O)_2NR^{16}R^{17}$, $-(CH_2)_nS(O)_2R^{16}$, halogen, –CN, $-(CH_2)_n$–aryl, $-(CH_2)_n$–heteroaryl, $-(CH_2)_nNH_2$, $-(CH_2)_nNHR^{16}$, and $-(CH_2)_nNR^{16}R^{17}$; optionally substituted;

R^{11} is selected from the group consisting of hydrogen, C_1–C_6-alkyl, $-CF_3$, C_2-C_6–alkenyl, C_2–C_8-alkynyl, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_n$–aryl, $-(CH_2)_n$–heterocycloalkyl and $-(CH_2)_n$–heteroaryl; optionally substituted;

X is selected from the group consisting of CH_2, C(O), C(S), CH(OH), $CH(OR^{16})$, $S(O)_2$, $-S(O)_2$–N(H)–, $-S(O)_2$–$N(R^{16})$–, –N(H)–$S(O)_2$–, $-N(R^{16})$–$S(O)_2$–, C(=NH), $C(=N–R^{16})$, $CH(NH_2)$, $CH(NHR^{16})$, $CH(NR^{16}R^{17})$, –C(O)–N(H)–, $-C(O)–N(R^{16})$–, –N(H)–C(O)–, $-N(R^{16})$–C(O)–, N(H), $N(–R^{16})$ and O;

R^{12} is selected from the group consisting of C_1–C_6-alkyl, $-CF_3$, C_2-C_6-alkenyl, C_2-C_8-alkynyl, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_n$–heterocycloalkyl, $-(CH_2)_n$–aryl, $-NR^{16}R^{17}$, and $-(CH_2)_n$–heteroaryl; optionally substituted;

R^{16} and R^{17} are independently selected from the group consisting of C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2–C_6-alkynyl, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_n$–aryl, $-CF_3$, $-C(O)R^{18}$ and $-S(O)_2R^{18}$; optionally substituted;

R^{18} is independently selected from the group consisting of C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2–C_6-alkynyl, $-(CH_2)_n$–cycloalkyl and $-CF_3$; optionally substituted; and

n is in each instance selected from 0, 1 and 2.

In the context of WO2011/000566 the term "optionally substituted" in each instance refers to between 1 and 10 substituents, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 substituents which are in each instance preferably independently selected from the group consisting of halogen, in particular F, Cl, Br or I; $-NO_2$, –CN, –OR', –NR'R",

–(CO)OR', –(CO)OR'", –(CO)NR'R", –NR'COR"", –NR'COR', –NR"CONR'R", –NR"SO_2A, –COR'"; –SO_2NR'R", –OOCR'", –CR'"R""OH, –R'"OH, =O, and –E;

R' and R" are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, –OE, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and aralkyl or together form a heteroaryl, or heterocycloalkyl; optionally substituted;

R'" and R"" are each independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, aralkyl, heteroaryl, and –NR'R"; and

E is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkoxy, alkoxyalkyl, heterocycloalkyl, an alicyclic system, aryl and heteroaryl; optionally substituted.

Widespread resistance to both classes of licensed influenza antivirals (M2 ion channel inhibitors (adamantanes) and neuraminidase inhibitors (Oseltamivir)) occurs in both pandemic and seasonal viruses, rendering these drugs to be of marginal utility in the treatment modality. For M2 ion channel inhibitors, the frequency of viral resistance has been increasing since 2003 and for seasonal influenza A/H3N2, adamantanes are now regarded as ineffective. Virtually all 2009 H1N1 and seasonal H3N2 strains are resistant to the adamantanes (rimantadine and amantadine), and the majority of seasonal H1N1 strains are resistant to oseltamivir, the most widely prescribed neuraminidase inhibitor (NAI). For oseltamivir the WHO reported on significant emergence of influenza A/H1N1 resistance starting in the influenza season 2007/2008; and for the second and third quarters of 2008 in the southern hemisphere. Even more serious numbers were published for the fourth quarter of 2008 (northern hemisphere) where 95% of all tested isolates revealed no Oseltamivir-susceptibility. Considering the fact that now most national governments have been stockpiling Oseltamivir as part of their influenza pandemic preparedness plan, it is obvious that the demand for new, effective drugs is growing significantly. To address the need for more effective therapy, preliminary studies using double or even triple combinations of antiviral drugs with different mechanisms of action have been undertaken. Adamantanes and neuraminidase inhibitors in combination were analysed in vitro and in vivo and found to act highly synergistically. However, it is known that for both types of antivirals resistant viruses

emerge rather rapidly and this issue is not tackled by combining these established antiviral drugs.

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. These two targets are located within distinct subunits of the polymerase complex and thus represent unique drug targets. Due to the fact that both functions are required for the so-called "cap-snatching" mechanism mandatory for viral transcription, concurrent inhibition of both functions is expected to act highly synergistically. This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles.

Both of these active sites are composed of identical residues in all influenza A strains (e.g., avian and human) and hence this high degree of sequence conservation underpins the perception that these targets are not likely to trigger rapid resistant virus generation. Thus, endonuclease and cap-binding inhibitors individually and in combination are ideal drug candidates to combat both seasonal and pandemic influenza, irrespectively of the virus strain.

The combination of an endonuclease inhibitor and a cap-binding inhibitor or a dual specific polymerase inhibitor targeting both the endonuclease active site and the cap-binding domain would be effective against virus strains resistant against adamantanes and neuraminidase inhibitors and moreover combine the advantage of low susceptibility to resistance generation with activity against a broad range of virus strains.

(ii) The combination of inhibitors of different antiviral targets (particularly targeting influenza) focusing on the combination with (preferably influenza) polymerase inhibitors as dual or multiple combination therapy. Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different

antiviral target is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetics properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the first group of polymerase inhibitors is combined with at least one compound selected from the second group of polymerase inhibitors.

The first group of polymerase inhibitors which can be used in this type of combination therapy includes, but is not limited to, the compounds having the formula (A) and/or (C).

The second group of polymerase inhibitors which can be used in this type of combination therapy includes, but is not limited to, the compounds having the general formula (I), the compounds having the general formula (II), the compounds disclosed in WO 2011/000566, WO 2010/110231, WO 2010/110409, WO 2006/030807 or US 5,475,109 as well as flutimide and analogues, favipiravir and analogues, epigallocatechin gallate and analogues, as well as nucleoside analogs such as ribavirine.

(iii) The combination of polymerase inhibitors with neuramidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different extracellular antiviral target, especially the (e.g., viral) neuraminidase is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different

mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one neuramidase inhibitor.

The neuraminidase inhibitor (particularly influenza neuramidase inhibitor) is not specifically limited. Examples include zanamivir, oseltamivir, peramivir, KDN DANA, FANA, and cyclopentane derivatives.

(iv) The combination of polymerase inhibitors with M2 channel inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different extracellular and cytoplasmic antiviral target, especially the viral M2 ion channel, is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one M2 channel inhibitor.

The M2 channel inhibitor (particularly influenza M2 channel inhibitor) is not specifically limited. Examples include amantadine and rimantadine.

(v) The combination of polymerase inhibitors with alpha glucosidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target, with an inhibitor of a different extracellular target, especially alpha glucosidase, is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the above-mentioned first group of polymerase inhibitors is combined with at least one alpha glucosidase inhibitor.

The alpha glucosidase inhibitor (particularly influenza alpha glucosidase inhibitor) is not specifically limited. Examples include the compounds described in Chang et al., Antiviral Research 2011, 89, 26-34.

(vi) The combination of polymerase inhibitors with ligands of other influenza targets

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of different extracellular, cytoplasmic or nucleic antiviral targets is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one ligand of another influenza target.

The ligand of another influenza target is not specifically limited. Examples include compounds acting on the sialidase fusion protein, e.g. Fludase (DAS181), siRNAs and phosphorothioate oligonucleotides, signal transduction inhibitors (ErbB tyrosine kinase, Abl kinase family, MAP kinases, PKCa-mediated activation of ERK signaling as well as interferon (inducers).

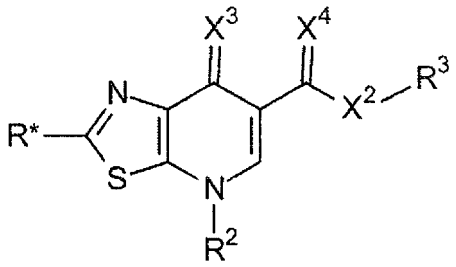
(vii) The combination of (preferably influenza) polymerase inhibitors with a compound used as an adjuvance to minimize the symptoms of the disease (antibiotics, anti-inflammatory agents like COX inhibitors (e.g., COX-1/COX-2 inhibitors, selective COX-2 inhibitors), lipoxygenase inhibitors, EP ligands (particularly EP4 ligands), bradykinin ligands, and/or cannabinoid ligands (e.g., CB2 agonists). Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a

polymerase inhibitor specifically addressing a viral intracellular target with an compound used as an adjuvance to minimize the symptoms of the disease address the causative and symptomatic pathological consequences of viral infection. This combination is expected to act synergistically because these different types of drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Compounds having the general formula (A)

The compounds having the general formula (A) are identified in the following.



(A)

The present invention provides a compound having the general formula (A) in which the following definitions apply.

R^* is –H, –Hal, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), $-C_{1-4}$ alkyl–(optionally substituted aryl) or $-X^1-R^1$. In a preferred embodiment, R^* is –Hal, –(optionally substituted C_{1-6} alkyl) (wherein the optional substituent of the alkyl group is preferably Hal, more preferably F); $-C_{1-4}$ alkyl–(optionally substituted aryl) (wherein the optional substituent of the aryl group is preferably halogen) or $-X^1-R^1$. In a more preferred embodiment R* is X^1-R^1.

X^1 is O, C(O), C(O)O, OC(O); S, SO, SO_2, NR^4, $N(R^5)C(O)$, $C(O)NR^5$, preferably X^1 is O, or NR^4, more preferably X^1 is NR^4. In one preferred embodiment, X^1 is NR^4 and R^1 and R^4 are joined together to form a 5- to 7-membered ring, which can optionally contain O, S or further N. In another preferred embodiment, X^1 is NR^4 and R^1 is $-SO_2-R^4$.

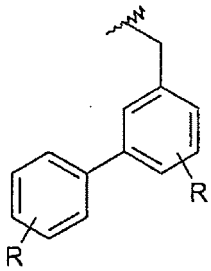
X^2 is O, S, NR^4, preferably X^2 is O.

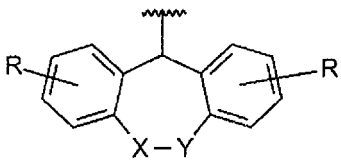
X^3 is O or S, preferably X^3 is O.

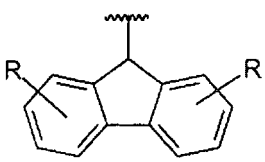
X^4 is O or S, preferably X^4 is O.

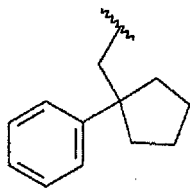
R^1 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), (optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), $-C_{1-4}$ alkyl–(optionally substituted aryl). Preferably R^1 is –H, –(optionally substituted C_{1-6} alkyl), -(optionally substituted benzyl), more preferably R^1 is –H or -(optionally substituted benzyl). Throughout the present specification, it is understood that the definitions of the substituents of the aryl group apply analogously to the benzyl group.

R^2 is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring, wherein the hydrocarbon group can be optionally substituted. Preferably, the at least one ring is aromatic such as an aryl or heteroaryl ring. More preferably, R^2 is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms and which contains at least two rings, wherein the hydrocarbon group can be optionally substituted. Even more preferably, at least one of the at least two rings is aromatic such as an aryl or heteroaryl ring. Preferred examples of R^2 can be selected from the group consisting of







and


wherein

X is absent, CH_2, NH, C(O)NH, S or O. Furthermore,

Y is CH_2.

In an alternative embodiment, X and Y can be joined together to form an annulated, carbo- or heterocylic 3- to 8-membered ring which can be saturated or unsaturated. Specific examples of X-Y include -CH_2-, -CH_2-CH_2-, -O-, and -NH-.

R is independently selected from H, –C_{1-6} alkyl, halogen, –CN, –OH, and –O–C_{1-6} alkyl.

R^3 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or –C_{1-4} alkyl–(optionally substituted aryl) or if X^2 is NR^4, then R^3 can also be –OH, preferably R^3 is –H, –C_{1-6} alkyl or Bz.

R^4 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), –C_{1-4} alkyl–(optionally substituted C_{3-7} cycloalkyl), or –C_{1-4} alkyl–(optionally substituted aryl) or if X^1 is NR^4, then R^4 and R^1 can be joined together to form a 5- to 7-membered ring, which can optionally contain O, S or further N or if X^2 is NR^4, then R^4 and R^3 can be joined together to form a 5- to 7-membered ring, which can optionally contain O, S or further N. Preferably, R^4 is –H, -(optionally substituted aryl), or –(optionally substituted C_{1-6} alkyl), more preferably, R^4 is –H or -(optionally substituted benzyl).

R^5 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), –C_{1-4} alkyl–(optionally substituted C_{3-7} cycloalkyl), or –C_{1-4} alkyl–(optionally substituted aryl). Preferably, R^5 is –H.

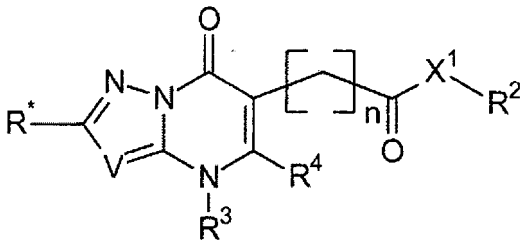
R^6 is –H, or –C_{1-6} alkyl.

The optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, –NR^6R^6, –OH, and –O–C_{1-6} alkyl. Preferably the substituent is –halogen, more preferably F.

The optional substituent of the cycloalkyl group, the aryl group or the hydrocarbon group is selected from the group consisting of –C_{1-6} alkyl, halogen, -CF_3, –CN, –X^1–R^5 and –C_{1-4} alkyl–aryl. Preferably, the substituent is -halogen (preferably F), -OCH_3 or -CN.

Compounds having the general formula (C)

The compounds having the general formula (C) are identified in the following.



(C)

It is understood that throughout the present specification the term "a compound having the general formula (C)" encompasses pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

In the present invention the following definitions apply with respect to the compounds having the general formula (C).

V is N, or CR^6.

X^1 is O, S, or NR^8, preferably X^1 is O.

X^2 is NR^5, $N(R^5)C(O)$, $C(O)NR^5$, O, C(O), C(O)O, OC(O); S, SO, SO_2, $SO_2N(R^5)$ or $N(R^5)SO_2$. Preferably, X^2 is NR^5 or $N(R^5)SO_2$.

R^* is –H, –Hal, –(optionally substituted C_{1-6} alkyl), –(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S), $-C_{1-4}$ alkyl–(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S), or $-X^2-R^1$. Preferably R^* is H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl) or $-X^2-R^1$.

R^1 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S), $-C_{1-4}$ alkyl–(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S). Preferably R^1 is $-C_{1-4}$ alkyl–(optionally

substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S).

R^2 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $-C_{1-4}$ alkyl–(optionally substituted aryl) or if X^1 is NR' then R^2 can also be –OH. Preferably, R^2 is -H or $-C_{1-6}$ alkyl.

R^3 is –H, $-R^7$, or $-X^2-R^7$. Preferably R^3 is –H, $-C_{1-4}$ alkyl–(optionally substituted aryl) or $-SO_2-R^5$. Preferably R^3 is –H.

R^4 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $-C_{1-4}$ alkyl–(optionally substituted aryl). Preferably, R^4 is –H, or –(optionally substituted C_{1-6} alkyl).

R^5 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $-C_{1-4}$ alkyl–(optionally substituted aryl). Preferably R^5 is $-C_{1-4}$ alkyl–(optionally substituted aryl) or -(optionally substituted C_{3-7} cycloalkyl).

R^6 H, $-C_{1-6}$ alkyl, –aryl, halogen or CN. Preferably, R^6 is H or -aryl.

R^7 is –(optionally substituted hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring). Preferably, R^7 is $-C_{1-4}$ alkyl–(optionally substituted aryl).

R^8 is –H, $-C_{1-6}$ alkyl or $-C_{1-4}$ alkyl–(optionally substituted aryl). Preferably, R^8 is $-C_{1-6}$ alkyl or $-C_{1-4}$ alkyl–(optionally substituted aryl).

n is 0 to 4, preferably 0 or 1.

The optional substituent of the alkyl group can be selected from the group consisting of halogen, –CN, $-NR^5R^5$, –OH, and $-O-C_{1-6}$ alkyl.

The optional substituent of the cycloalkyl group, the aryl group, the mono- or polycyclic group or the hydrocarbon group can be selected from the group consisting of $-C_{1-6}$ alkyl, halogen, $-CF_3$, –CN, $-X^2-C_{1-6}$ alkyl and $-C_{1-6}$ alkyl–aryl.

Various modifications and variations of the invention will be apparent to those skilled in the art without departing from the scope of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be covered by the present invention.

The following examples are merely illustrative of the present invention and should not be construed to limit the scope of the invention as indicated by the appended claims in any way.

EXAMPLES

FRET endonuclease activity assay

The influenza A virus (IAV) PA-Nter fragment (amino acids 1 – 209) harbouring the influenza endonuclease activity was generated and purified as described in Dias et al., Nature 2009; Apr 16; 458(7240), 914-918. The protein was dissolved in buffer containing 20mM Tris pH 8.0, 100mM NaCl and 10mM β-mercaptoethanol and aliquots were stored at –20 °C.

A 20 bases dual-labelled RNA oligo with 5′-FAM fluorophore and 3′-BHQ1 quencher was used as a substrate to be cleaved by the endonuclease activity of the PA-Nter. Cleavage of the RNA substrate frees the fluorophore from the quencher resulting in an increase of the fluorescent signal.

All assay components were diluted in assay buffer containing 20mM Tris-HCl pH 8.0, 100mM NaCl, 1mM $MnCl_2$, 10mM $MgCl_2$ and 10mM β-mercaptoethanol. The final concentration of PA-Nter was 0.5µM and 1.6µM RNA substrate. The test compounds were dissolved in DMSO and generally tested at two concentrations or a concentration series resulting in a final plate well DMSO concentration of 0.5 %. In those cases where the compounds were not soluble at that concentration, they were tested at the highest soluble concentration. SAV-6004 was used as a reference in the assay at a concentration of 0.1µM.

5µl of each compound dilution was provided in the wells of white 384-well microtiter plates (PerkinElmer) in eight replicates. After addition of PA-Nter dilution, the plates were sealed and incubated for 30min at room temperature prior to the addition of 1.6µM RNA substrate diluted in assay buffer. Subsequently, the increasing fluorescence signal of cleaved RNA was measured in a microplate reader (Synergy HT, Biotek) at 485nm excitation and 535nm emission wavelength. The kinetic read interval was 35sec at a sensitivity of 35. Fluorescence signal data over a period of 20min were used to calculate the initial velocity (v0) of substrate cleavage. Final readout was the % reduction of v0 of compound-treated samples compared to untreated. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the initial reaction velocities (v0) ina given concentration series ranging from maximum 100 µM to at least 2 nM.

Cytopathic effect (CPE) assay

The influenza A virus (IAV) was obtained from American Tissue Culture Collection (A/Aichi/2/68 (H3N2); VR-547). Virus stocks were prepared by propagation of virus on Mardin-Darby canine kidney (MDCK; ATCC CCL-34) cells and infectious titres of virus stocks were determined by the 50 % tissue culture infective dose ($TCID_{50}$) analysis as described in Reed, L. J., and H. Muench. 1938, Am. J. Hyg. 27:493-497.

MDCK cells were seeded in 96-well plates at 2×10^4 cells/well using DMEM/Ham's F-12 (1:1) medium containing 10 % foetal bovine serum (FBS), 2 mM L-glutamine and 1 % antibiotics (all from PAA). Until infection the cells were incubated for 5 hrs at 37 °C, 5.0 % CO_2 to form a ~80 % confluent monolayer on the bottom of the well. Each test compound was dissolved in DMSO and generally tested at 25 µM and 250 µM. In those cases where the compounds were not soluble at that concentration they were tested at the highest soluble concentration. The compounds were diluted in infection medium (DMEM/Ham's F-12 (1:1) containing 5 µg/ml trypsin, and 1 % antibiotics) for a final plate well DMSO concentration of 1 %. The virus stock was diluted in infection medium (DMEM/Ham's F-12 (1:1) containing 5 µg/ml Trypsin, 1 % DMSO, and 1 % antibiotics) to a theoretical multiplicity of infection (MOI) of 0.05.

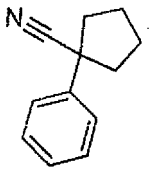
After removal of the culture medium and one washing step with PBS, virus and compound were added together to the cells. In the wells used for cytotoxicity determination (i.e. in the

absence of viral infection), no virus suspension was added. Instead, infection medium was added. Each treatment was conducted in two replicates. After incubation at 37 °C, 5 % CO_2 for 48 hrs, each well was observed microscopically for apparent cytotoxicity, precipitate formation, or other notable abnormalities. Then, cell viability was determined using CellTiter-Glo luminescent cell viability assay (Promega). The supernatant was removed carefully and 65 µl of the reconstituted reagent were added to each well and incubated with gentle shaking for 15 min at room temperature. Then, 60 µl of the solution was transferred to an opaque plate and luminescence (RLU) was measured using Synergy HT plate reader (Biotek).

Relative cell viability values of uninfected-treated versus uninfected-untreated cells were used to evaluate cytotoxicity of the compounds. Substances with a relative viability below 80 % at the tested concentration were regarded as cytotoxic and retested at lower concentrations.

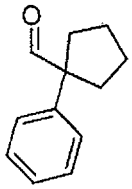
Reduction in the virus-mediated cytopathic effect (CPE) upon treatment with the compounds was calculated as follows: The response (RLU) of infected-untreated samples was subtracted from the response (RLU) of the infected-treated samples and then normalized to the viability of the corresponding uninfected sample resulting in % CPE reduction. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the RLU response in a given concentration series ranging from maximum 100 µM to at least 100 nM.

Example 1: Preparation of 1-phenyl-cyclopentanecarbonitrile



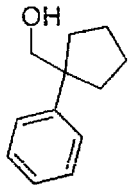
To a suspension of NaH (11.3 g, 281.7 mmol, 60 %) in DMSO (75 ml) were added dropwise a mixture of phenyl-acetonitrile (15 g, 128.0 mmol) and 1,4-dibromo-butane (18 ml, 128.0 mmol) dissolved in DMSO:Ether (150 ml, 1:1) at 0 °C and the reaction mixture was stirred at room temperature (RT) for 2 to 3 h. After completion of the reaction, water and 10% HCl solution were added to the crude mass. It was extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (10% EtOAc-hexane) to get 1-phenyl-cyclopentanecarbonitrile (2) (19 g, 86.64 %) as a yellow solid. MS: m/z = 171 (MH+).

Example 2: Preparation of 1-phenyl-cyclopentanecarbaldehyde



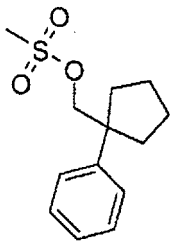
To a solution of 1-phenyl-cyclopentanecarbonitrile (17 g, 99.4 mmol) in DCM (200 ml) was added diisobutylaluminium hydride (DIBAL) (140 ml, 25% in toluene, 248.5 mmol) very slowly. The mixture was stirred at –70 °C for 2 h. After completion of the reaction, it was slowly quenched by the addition of aqueous potassium sodium tartrate solution and then the mixture was stirred at RT for 16 h. It was then extracted with dichloromethane (DCM), washed with water, brine and dried with Na_2SO_4. The organic phase was concentrated to provide 1-phenyl-cyclopentanecarbaldehyde as a colorless liquid (15.5 g, crude).

Exmaple 3: Preparation of (1-phenyl-cyclopentyl)-methanol



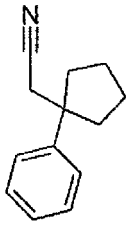
$NaBH_4$ (3.2 g, 86.2 mmol) was added portion wise to a cooled (ice bath) solution of 1-phenyl-cyclopentanecarbaldehyde (7.5 g, 43.1 mmol) in methanol (100 ml) and then stirred for 16 h at RT. After completion of the reaction, it was quenched with saturated ammonium chloride solution and the methanol under reduced pressure. The mixture was diluted with water, extracted with EtOAc, washed with water, brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (15% EtOAc in hexanes) provided (1-phenyl-cyclopentyl)-methanol as a white solid (6 g, 79.8%).

Example 4: Preparation of methanesulfonic acid 1-phenyl-cyclopentylmethyl ester



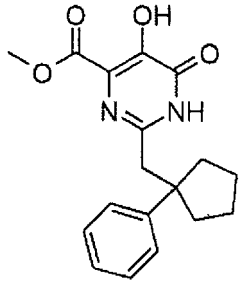
To a solution of (1-phenyl-cyclopentyl)-methanol (11.5 g, 64.34 mmol) in DCM (100 ml) was added TEA (17.5 ml, 130.68 mmol) and followed by methanesulfonyl chloride (MsCl) (8.9 g, 78.4 mmol) was added drop wise at 0 °C and the reaction mixture was stirred at RT for 16 h. After completion of the reaction, it was quenched with water and concentrated. Then the crude product was dissolved in DCM, extracted with DCM and the organic layer was washed with water, and brine and then dried over Na_2SO_4. The combined organic layer was concentrated to get crude methanesulfonic acid 1-phenyl-cyclopentylmethyl ester (10 g, crude) as a white solid.

Example 5: Preparation of (1-phenyl-cyclopentyl)-acetonitrile



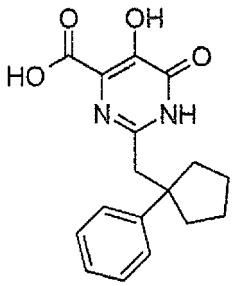
To a stirred solution of methanesulfonic acid 1-phenyl-cyclopentylmethyl ester (10 g, 39.37 mmol) in DMSO (30 ml) were added KI (0.6 g, 3.9 mmol) and NaCN (2.89 g, 59.05 mmol). It was then stirred at 140 °C for 16 h. After completion of the reaction, it was diluted with water, extracted with EtOAc and the organic layer was washed with water and brine. It was then dried over Na_2SO_4, concentrated and purified by normal column chromatography (15% EtOAc in hexanes) to afford the title compound as a colorless liquid (2.5 g, 34%).

Example 6: Preparation of 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



A solution of potassium hydroxide (10.8 ml, 10.8 mmol) in methanol and hydroxylamine hydrochloride (10.8 ml, 10.8 mmol) in methanol were mixed, filtered and added to 2-(1-phenylcyclopentyl)acetonitrile (1 g, 5.4 mmol) in methanol (MeOH) and stirred at 60 °C for 24 h. It was then evaporated to dryness. The residue was dissolved in chloroform (30 ml) and to this was added dimethyl but-2-ynedioate (844 mg, 5.94 mmol). The reaction mixture was The mixture was stirred at 60 °C for 24 h, cooled and evaporated to dryness. The residue was dissolved in xylene (10 ml) and heated at 140 °C in a microwave oven for 1 h. The cooled residue was evaporated to dryness. Chromatography was conducted (40 g SiO_2; 10 to 70% EtOAc in hexanes). The residue was triturated with EtOAc, filtered and washed with Et_2O and dried under vacuum to give the title product as an off-white solid (0.110 g; 6%). LCMS: m/z = 329 (MH+).

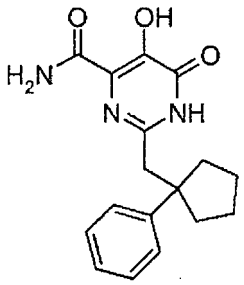
Example 7: Preparation of 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid.



A solution of lithium hydroxide (7.66 mg, 320 µmol) in water (1.00 ml) was added to a stirred mixture of methyl 5,6-dihydroxy-2-((1-phenylcyclopentyl)methyl)pyrimidine-4-carboxylate (0.035 g, 107 µmol) in tetrahydrofuran (THF) (4 ml). The mixture was stirred at RT for 72 h

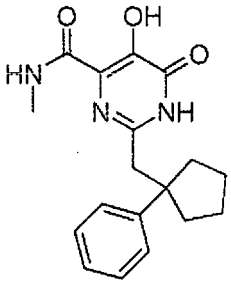
and then quenched with amberlyst (H+) IE resin, filtered and evaporated to dryness. The residue was triturated with EtOAc and dried under vacuum to give the title product as a white solid (0.012 g; 32%). LCMS: m/z = 315 (MH+).

Example 8: Preparation of 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid amide



A solution of methyl 5,6-dihydroxy-2-((1-phenylcyclopentyl)methyl)pyrimidine-4-carboxylate (0.020 g, 60.9 µmol) in ammonia in MeOH (435 µl, 3.05 mmol) was heated at 100 °C for 20 min. The cooled solution was evaporated to dryness. The residue was diluted with MeOH and heated in the presence of Amberlyst resin (H+) until in solution. The material was filtered to remove the resin and evaporated to dryness. Trituration with MeOH followed by washing with Et_2O provided the desired product as a white solid (0.011 g; 49%). LCMS: m/z = 314 (MH+).

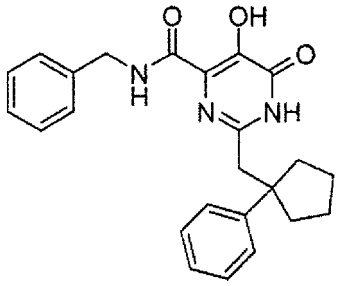
Example 9: Preparation of 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



To a solution of 5,6-dihydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid methyl ester (55 mg, 0.167 mmol) in THF (2 ml) was added 2M solution of methyl amine in THF (0.419 mL, 0.838 mmol) under nitrogen atmosphere in a microwave vessel. The reaction mixture was heated in a microwave oven at 110 °C for 10 min, then cooled and evaporated to

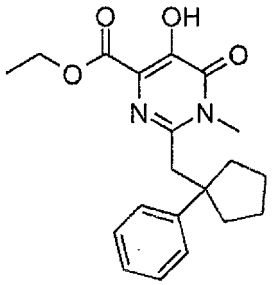
dryness. The residue was washed with water and 30% ethyl acetate in hexane to get the title compound as an off-white solid (0.020 g, 36%). LCMS: m/z = 327.8 (MH+).

Example 10: Preparation of 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid benzylamide



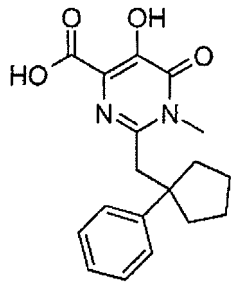
5,6-Dihydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid benzylamide was synthesized as an off-white solid (20 mg, 30%) from 55 mg of 5,6-dihydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid methyl ester following the procedure described for 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide (Example 9). LCMS: m/z = 403.8 (MH+).

Example 11: Preparation of 5-hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester



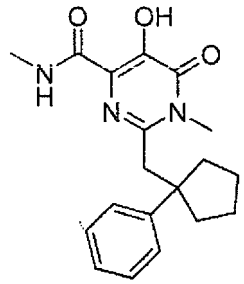
5-Hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester was synthesized as a brown solid (35 mg, 20%) from 200 mg of 5-ethoxycarbonylmethyl-2-methyl-3-(1-phenyl-cyclopentylmethyl)-2,5-dihydro-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester following the procedure described for 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (Example 6). LCMS: m/z = 357.0 (MH+).

Example 12: Preparation of 5-hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid



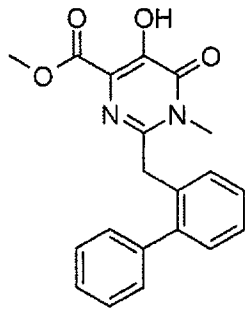
5-Hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl acid was synthesized as a white solid (30 mg, 23.2%) from 140 mg of 5-hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester following the procedure described for 5-hydroxy-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid (Example 7). LCMS: m/z 327.0 (M-H).

Example 13: Preparation of 5-hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



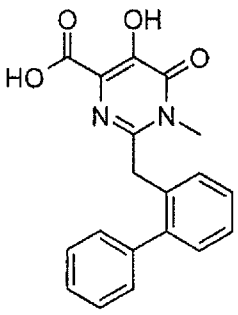
To a mixture of 5-hydroxy-1-methyl-6-oxo-2-(1-phenyl-cyclopentylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester (175 mg, 0.491 mmol) and methyl amine (0.98 ml, 1.96 mmol, 2M in THF) was added a catalytic amount of Me_3Al under argon atmosphere in a sealed tube and it was heated at 60°C for 16 h. After completion of the reaction, it was quenched with ice slowly and then extracted with EtOAc. The combined organic layer was then washed with water and brine. It was then dried over Na_2SO_4 and concentrated under vacuum. Purification by preparative HPLC provided the title compound as an off-white solid (40 mg, 24%). LCMS: m/z = 342.0 (MH+).

Example 14: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



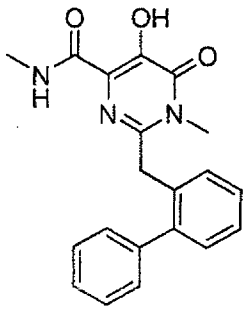
A mixture containing 2-(biphenyl-2-yl)acetonitrile (2 g, 10.3 mmol), sodium carbonate (329 mg, 3.1 mmol) and N-methylhydroxylamine hydrochloride (432 mg, 5.17 mmol) in ethanol (5 ml) and water (5 ml) was heated at 80°C for 2 h, cooled and treated with dimethyl but-2-ynedioate (809 mg, 5.69 mmol). The mixture was stirred at room temperature for 5 h and then diluted with EtOAc, washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. Chromatography (40 g SiO_2, 10 to 60% EtOAc in hexanes) provided the 1,2,4-oxadiazoline intermediate as an orange oil. The oil was diluted in xylene (5.00 ml) and heated at 130 °C in a microwave oven for 3.5 h. The cooled mixture was diluted with EtOAc, washed with brine, dried ($MgSO_4$) and evaporated to dryness. Chromatography (24 g SiO_2; 20 to 60% EtOAc in hexanes) gave the title compound as a light brown foam (0.43 g; 81%). LCMS: m/z = 351 (MH+).

Example 15: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid



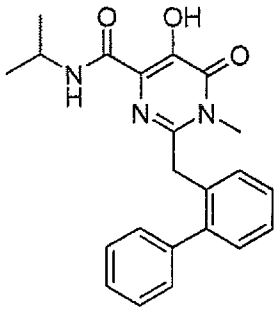
A solution of lithium hydroxide (8.2 mg, 342 µmol) in water was added to a stirred solution of methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.1 g, 285 µmol) in THF. After 24 h, the reaction was quenched by addition of 1M HCl, extracted into EtOAc, washed with brine, dried ($MgSO_4$) and evaporated. Purification by preparative HPLC gave the desired product as a white solid (0.010 g; 10%). LCMS: m/z = 337 (MH+).

Example 16: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



A sealed tube containing 2M solution of methylamine (1.71 ml, 3.42 mmol) in THF and methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.1 g, 285 µmol) was heated at 100 °C in a microwave oven for 20 min, cooled and filtered. The solid was stirred in MeOH, in the presence of Amberlyst 15 IE resin, at 60 °C for 5 min and then at room temperature for 1 h, filtered, evaporated to dryness and triturated with Et_2O to give the title compound as a white solid (0.040 g; 40%). LCMS: m/z = 351 (MH+).

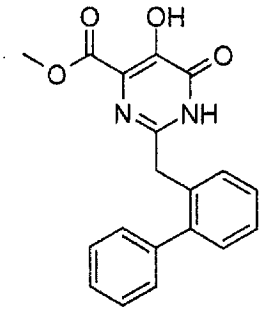
Example 17: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid isopropylamide



A sealed tube containing propan-2-amine (202 mg, 292 µl, 3.42 mmol), methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.1 g, 285 µmol)

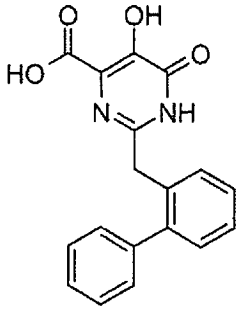
and THF (1.7 ml) was heated at 110 °C in a microwave oven for 20 minutes. The crude reaction mixture was cooled and evaporated to dryness. Purification by preparative HPLC provided the desired product as a light pink solid (0.015 g; 14%). LCMS: m/z = 379 (MH+).

Example 18: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



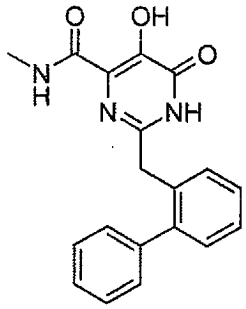
A 1M solution of hydroxylamine hydrochloride in MeOH (15 ml) and 1M KOH solution in MeOH (15 ml) was combined at 0 °C. After 10 minutes, the salt was removed by filtration and the filtrate was directly added to a flask containing 2-(biphenyl-2-yl)acetonitrile (0.50 g, 2.58 mmol) and was heated at 60 °C overnight. The cooled mixture was evaporated to dryness under reduced pressure and the residue was dissolve in EtOAc, washed with water, and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in chloroform (10 ml) and treated with dimethyl but-2-ynedioate (0.403 g, 2.84 mmol). The mixture was stirred at 60 °C for 1 h and then evaporated to dryness. The residue was diluted with xylenes (10 ml) and heated at 130 °C for 90 min. The cooled filtrate was filtered, triturated with EtOAc and dried under vacuum to give the title product as an off-white solid (0.161 g; 18%). LCMS: m/z = 337 (MH+).

Example 19: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid



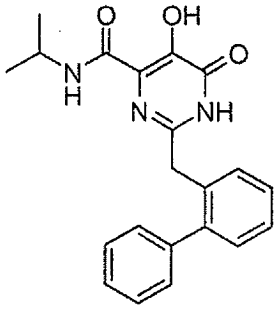
The title product was prepared according to Example 15 using 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.050 g; 0.148 mmol). The title compound was produced as an off-white solid (0.020 g; 41%). LCMS: m/z = 321 (M-H).

Example 20: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



A sealed tube containing 2M solution of methylamine (2 ml, 4 mmol) in THF and methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.05 g, 163 µmol, Eq: 1.00) was heated at 150 °C in a microwave oven for 15 min, cooled and filtered. The solid was stirred in MeOH, in the presence of Amberlyst 15 IE resin, at 60°C for 5 min and then at room temperature for 1 h, filtered, evaporated to dryness and triturated with Et_2O to give the title compound as a white solid (0.015 g; 27%). LCMS: m/z = 336 (MH+).

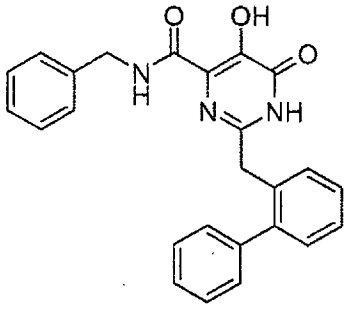
Example 21: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid isopropylamide



A sealed tube containing propan-2-amine (347 mg, 500 µl, 5.87 mmol), methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.50 g, 148 µmol) was heated at 150 °C in a microwave oven for 10 minutes. The crude reaction mixture was cooled and

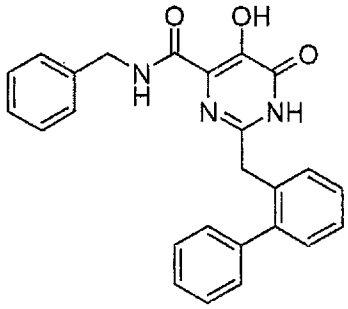
evaporated to dryness. The solid residue was stirred in MeOH, in the presence of Amberlyst 15 IE resin, at 60 °C for 5 min and then at room temperature for 1 h, filtered, evaporated to dryness and triturated with Et_2O to give the title compound as a white solid (0.012 g; 22%). LCMS: m/z = 364 (MH+).

Example 22: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid benzylamide



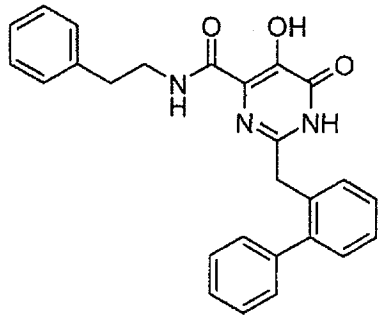
The synthesis was performed as in Example 21 using methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.070 g, 208 µmol) and benzylamine (0.5 ml; 4.58 mmol) to provide the title compound as an off-white solid (0.055 g; 64%). LCMS: m/z = 412 (MH+).

Example 23: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid-4-fluorobenzylamide



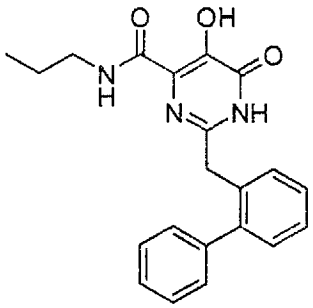
The synthesis performed as in Example 21 using methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.070 g, 208 µmol) and 4-fluorobenzylamine (0.5 ml; 4.38 mmol) to provide the title compound as an off-white solid (0.016 g; 18%). LCMS: m/z = 430 (MH+).

Example 24: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid phenethylamide



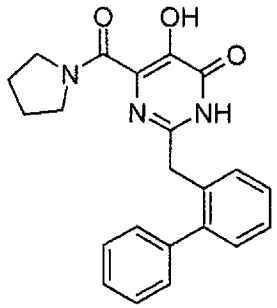
The synthesis was performed as in Example 21 using methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.10 g, 298 µmol) and phenethylamine (0.5 ml; 3.98 mmol) to provide the title compound as an off-white solid (0.054 g; 42%). LCMS: m/z = 425 (MH+).

Example 25: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid isopropylamide



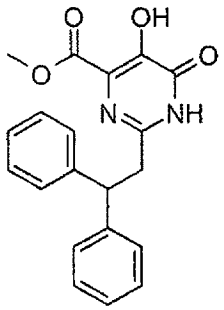
The synthesis was performed as in Example 21 using methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.10 g, 298 µmol) and isopropylamine (0.5 ml; 6.10 mmol) to provide the title compound as an off-white solid (0.059 g; 54%). LCMS: m/z = 412 (MH+).

Example 26: Preparation of 2-biphenyl-2-ylmethyl-5-hydroxy-6-(pyrrolidine-1-carbonyl)-3H-pyrimidin-4-one



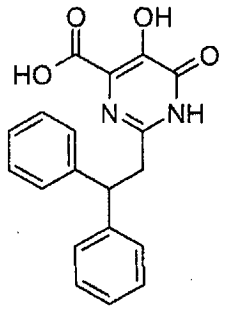
The synthesis was performed as in Example 21 using methyl 2-(biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.10 g, 298 µmol) and pyrrolidine (0.5 ml; 6.06 mmol) to provide the title compound as an off-white solid (0.059 g; 54%). LCMS: m/z = 412 (MH+). LCMS: m/z = 375 (MH+).

Example 27: Preparation of 2-(2,2-diphenyl-ethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



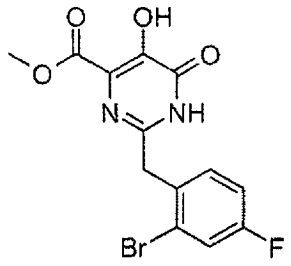
A solution of hydroxylamine hydrochloride (38.6 ml, 38.6 mmol) in MeOH was added to a solution of potassium hydroxide (38.6 ml, 38.6 mmol, Eq: 4) in MeOH at 0 °C. The resulting mixture was filtered and the filtrate was added to a 150 mL round-bottomed flask containing 3,3-diphenylpropanenitrile (2 g, 9.65 mmol). The mixture was heated at reflux for 16 h, cooled and evaporated to dryness. The residue was dissolved in EtOAc, washed with brine, dried ($MgSO_4$) and evaporated to dryness. The crude product was dissolved in $CHCl_3$ (50 ml), treated with dimethyl but-2-ynedioate (1.65 g, 11.6 mmol, Eq: 1.2) and heated at reflux for 1h and then evaporated to dryness. The residue was dissolved in xylene (10 ml), heated at 120 °C in a microwave oven for 4 h and evaporated to dryness. Chromatography (80 g SiO_2; 20 to 100% EtOAc in hexanes) gave the title product as an off-white solid (0.42; 12%). LCMS: m/z = 348.9 (MH+).

Example 28: Preparation of 2-(2,2-diphenyl-ethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid



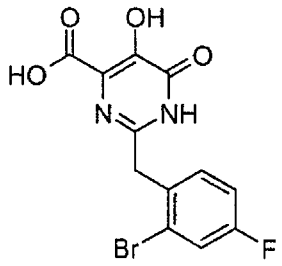
A solution of lithium hydroxide (21.9 mg, 913 µmol) in water (2 ml) was added to a flask containing a stirred solution of 2-(2,2-diphenyl-ethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.160 g, 457 µmol) in THF (8 ml). The mixture was stirred at room temperature for 8 h, quenched with 1M HCl, extracted into EtOAc, washed with brine, dried ($MgSO_4$) and evaporated to dryness. Purification by preparative HPLC provided the desired product as a white solid (0.024 g; 15%). LCMS: m/z = 337 (MH+).

Example 29: Preparation of 2-(2-bromo-4-fluoro-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



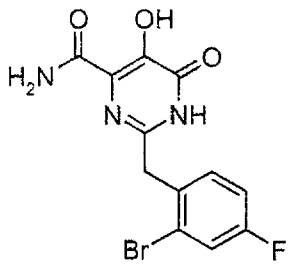
A solution of potassium hydroxide (18.7 ml, 18.7 mmol) in methanol and hydroxylamine hydrochloride (18.7 ml, 18.7 mmol) in methanol were mixed, filtered and added to 2-(2-bromo-4-fluorophenyl)acetonitrile (1 g, 4.67 mmol) in MeOH and stirred at 60°C for 24 h, evaporated to dryness. The residue was dissolved in chloroform (30.0 ml) and to this was added dimethyl but-2-ynedioate (730 mg, 5.14 mmol). The mixture was stirred at 60°C for 24 h, cooled and evaporated to dryness. The residue was dissolved in xylene (10 ml) and heated at 120°C for 2 h in microwave oven. The cooled residue was evaporated to dryness and then triturated with EtOAc, filtered and washed with Et_2O to give the title compound as a brown solid (0.21 g; 12%). LCMS: m/z = 358 (MH+).

Example 30: Preparation of 2-(2-bromo-4-fluoro-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid



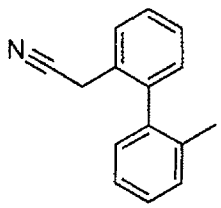
A solution of lithium hydroxide monohydrate (23.5 mg, 560 µmol) in water (1 ml) was added to a stirred solution of methyl 2-(2-bromo-4-fluorobenzyl)-5,6-dihydroxypyrimidine-4-carboxylate (50 mg, 140 µmol) in THF (4 ml). The resulting mixture was stirred at room temperature for 24 h. The mixture was then acidified by the addition of Amberlyst resin, filtered and evaporated to dryness. The residue was triturated with Et_2O to give the title compound as a white solid (0.02 g; 41%). LCMS: m/z = 344 (MH+).

Example 31: Preparation of 2-(2-bromo-4-fluoro-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid amide



A solution of ammonia in MeOH (1 mL, 7.00 mmol) was added to a flask containing methyl 2-(2-bromo-4-fluorobenzyl)-5,6-dihydroxypyrimidine-4-carboxylate (50 mg, 140 µmol). The mixture was heated at 120°C for 15 minutes in a microwave oven. The resulting product was collected by filtration, suspended in MeOH with Amberlyst resin and heated. The warm mixture was filtered and evaporated to dryness. The residue was triturated with Et_2O and dried under vacuum to give the title compound as a white solid (0.032 g; 67%). LCMS: m/z = 343 (MH+).

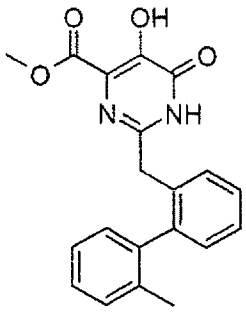
Example 32: Preparation of (2'-methyl-biphenyl-2-yl)-acetonitrile



In a vial, 2-bromophenylacetonitrile (2 g, 10.2 mmol), 2-methylphenylboronic acid (1.53 g, 11.2 mmol) and potassium carbonate (2.82 g, 20.4 mmol, Eq: 2) were combined with toluene (15.0 ml), ethanol (15 ml) and water (5 ml) to give a light brown suspension. The mixture was degassed with argon and then tetrakis(triphenylphosphine)palladium(0) (354 mg, 306 µmol) was added. The reaction mixture was heated at 90°C for 12 h, cooled and poured into water and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (silica gel, 0% to 5% EtOAc in hexanes) provided the title product as a colourless oil (1.57 g; 74%).

^{1}H NMR (300 MHz; $CDCl_3$) δ ppm 2.06 (s, 3 H), 3.43 (s, 2 H), 7.07-7.61 (m, 8 H).

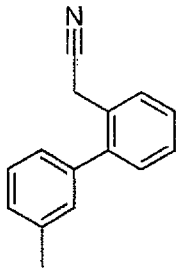
Example 33: Preparation of 5-hydroxy-2-(2'-methyl-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



A solution of hydroxylamine hydrochloride (979 mg, 14.1 mmol) in methanol (15 ml) and a solution of potassium hydroxide (790 mg, 14.1 mmol) in methanol (15 ml) were combined at 0°C. Solid (KCl) was removed by filtration. The filtrate was added to 2-(2'-methylbiphenyl-2-yl)acetonitrile (1.46 g, 7.04 mmol) and heated at 60°C overnight. An extra equivalent of NH_2OH in MeOH solution was added and heating was continued for 5 h. The mixture was cooled and then concentrated in vacuo. The residue was taken up into $CHCl_3$ (30 ml) and to this was added dimethyl acetylenedicarboxylate (1.00 g, 7.04 mmol). The mixture was heated at 60°C overnight, cooled and evaporated. The residue was transferred to a microwave vial and xylene (8 ml) was added. The vial was capped and heated in the microwave oven at

140°C for 3 h, cooled. Chromatography (silica gel; 10% to 100% EtOAc in hexanes) provided the desired product as an off-white solid (0.003 g; 0.12%). LCMS: m/z = 351 (MH+).

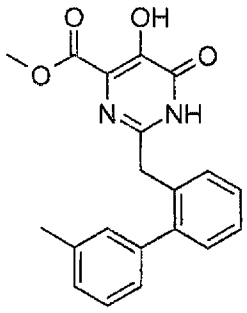
Example 34: Preparation (3'-methyl-biphenyl-2-yl)-acetonitrile



In a vial, 2-bromophenylacetonitirle (2 g, 10.2 mmol), m-tolylboronic acid (1.66 g, 12.2 mmol) and potassium carbonate (2.82 g, 20.4 mmol) were combined with toluene (15 ml), ethanol (15 ml) and water (5 ml) to give a light brown suspension. The mixture was degassed with argon and then tetrakis(triphenylphosphine)palladium(0) (354 mg, 306 µmol) was added. The reaction mixture was heated to 90°C and stirred overnight. The resulting cooled mixture was diluted with water and extracted into EtOAc. The organic phase was separated and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel; 0% to 5% EtOAc in hexanes) provided the title product as a colourless oil (1.82 g; 80%).

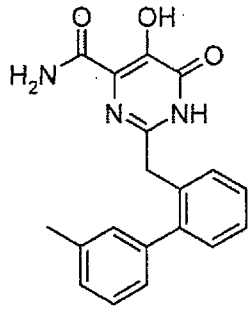
^{1}H NMR (300 MHz; $CDCl_3$) δ ppm 2.42 (s, 3 H), 3.65 (s, 2 H), 7.03-7.62 (m, 8 H).

Example 35: Preparation of 5-hydroxy-2-(3'-methyl-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



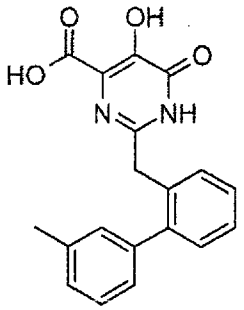
The compound was prepared using the same general procedure as Example 32 using 2-(3'-methylbiphenyl-2-yl)acetonitrile (1.81 g, 8.73 mmol). The title product was isolated as a white solid (0.07 g; 2%). LCMS: m/z = 351 (MH+).

Example 36: Preparation of 5-hydroxy-2-(3'-methyl-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid amide



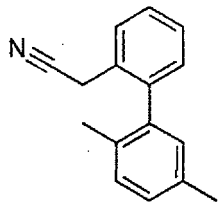
A mixture containing methyl 5-hydroxy-2-((3'-methylbiphenyl-2-yl)methyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (55 mg, 157 µmol) and ammonia (7M in MeOH) (4 ml, 28.0 mmol) in MeOH (2 ml) was heated at 100°C overnight. The cooled reaction mixture was concentrated in vacuo and then triturated from methanol to give the title product as an off-white solid (0.025 g; 47%). LCMS: m/z = 336 (MH+).

Example 37: Preparation of 5-hydroxy-2-(3'-methyl-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid



In a round-bottomed flask, methyl 5-hydroxy-2-((3'-methylbiphenyl-2-yl)methyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (30 mg, 85.6 µmol) and lithium hydroxide hydrate (6.5 mg, 155 µmol) were combined with THF (2 ml) and water (1 ml) to give a colorless solution. The mixture was stirred at 50°C for one day. Amberlyst (15, ion exchange resin) was added, the mixture was stirred for 10 min, filtered and evaporated to dryness. Trituration with EtOAc and hexanes provided the title compound as a white solid (0.011 g; 34%). LCMS: m/z = 337 (MH+) 90% pure.

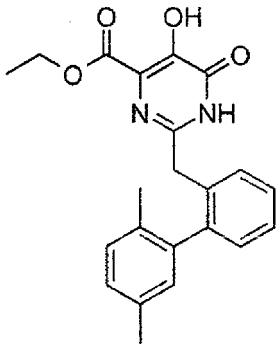
Example 38: Preparation of (2',5'-dimethyl-biphenyl-2-yl)-acetonitrile



The compound was prepared using the same general procedure as Example 33 using 2,5-dimethylphenylboronic acid (4.21 g, 28.1 mmol, Eq: 1.1). The title compound was prepared as a colourless oil (4.7 g; 83%).

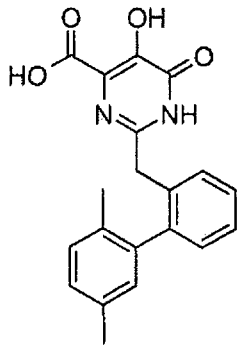
^{1}H NMR (300 MHz; $CDCl_3$) δ ppm 2.01 (s, 3 H), 2.35 (s, 3 H), 3.44 (s, 2 H), 6.96 (s, 1 H), 7.08-7.24 (m, 3 H), 7.34-7.47 (m, 2 H), 7.53-7.62 (mm 1 H).

Example 39: Preparation of 2-(2',5'-dimethyl-biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester



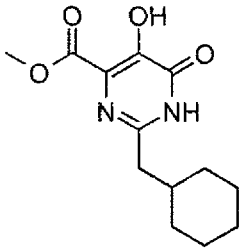
The compound was prepared using the same general procedure as Example 32 using 2-(2',5'-dimethylbiphenyl-2-yl)acetonitrile (4.7 g, 21.2 mmol) and diethyl but-2-ynedioate (3.61 g, 21.2 mmol). The title product was isolated as a white solid (0.84 g; 10%). LCMS: m/z = 379 (MH+).

Example 40: Preparation of 2-(2',5'-dimethyl-biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid



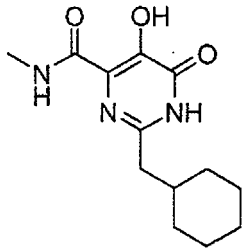
The compound was prepared according to the same procedure as in Example 29 using 2-(2',5'-dimethyl-biphenyl-2-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester (22 mg, 58.1 µmol) to provide the title compound as an off-white solid (0.018 g; 95% pure, 84% yield). LCMS: m/z = 349 (M-H).

Example 41: Preparation of 2-cyclohexylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



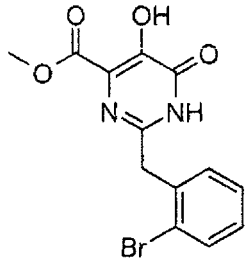
The compound was prepared according to the same procedure as in Example 32 using 2-cyclohexylacetonitrile (2.5 g, 20.3 mmol). The title product was isolated as a white solid (0.060 g; 1%). LCMS: m/z = 280 (MH+).

Example 42: Preparation of 2-cyclohexylmethyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



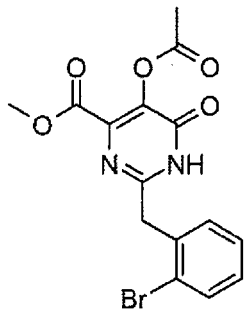
A mixture of methyl 2-(cyclohexylmethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (30 mg, 113 µmol), methylamine (2M in THF) (1.5 ml, 3.00 mmol) and MeOH (10 ml) was heated in a microwave oven at 140°C for 40 min. The cooled reaction mixture was concentrated in vacuo. The residue was heated in a mixture of MeOH and Amberlyst until all the product had dissolved. The resin was removed by filtration and the filtrate was evaporated to dryness under reduced pressure to give the title compound as an off-white solid (0.011 g; 35% with 95% purity). LCMS: m/z = 266 (MH+).

Example 43: Preparation of 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



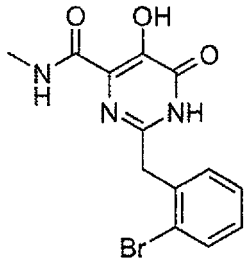
The compound was prepared according to the same procedure as in Example 18 using 2-(2-bromophenyl)acetonitrile (0.50 g, 2.5 mmol) and dimethylacetylenedicarboxylate (0.40g, 2.81 mmol). This provided the title product as a white solid (0.084 g; 9%). LCMS: m/z = 340 (MH+).

Example 44: Preparation of 5-acetoxy-2-(2-bromo-benzyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



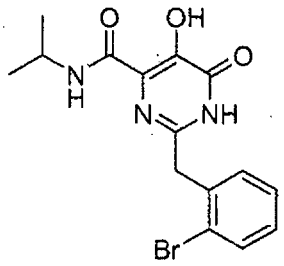
In a round-bottomed flask, methyl 2-(2-bromobenzyl)-5,6-dihydroxypyrimidine-4-carboxylate (300 mg, 885 µmol) was combined with DCM (10 ml) to give a brown suspension. Acetyl chloride (1M in DCM) (2.21 ml, 2.21 mmol) was added slowly at room temperature. The mixture was stirred for one hour and then poured onto aqueous saturated NH_4Cl solution and extracted with DCM. The organic phase was washed with brine solution, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Chromatography (SiO_2; DCM) provided the title product as a white solid (0.33 g; 97%). LCMS: m/z = 381/383 (MH+).

Example 45: Preparation of 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



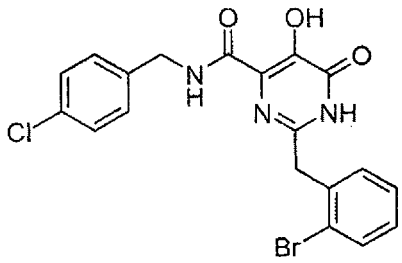
The compound was prepared according to the same procedure as in Example 20 using 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.08 g; 0.236 mmol). This gave the title compound as a white solid (0.032 g; 40%). LCMS: m/z = 339 (MH+).

Example 46: Preparation of 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid isopropylamide



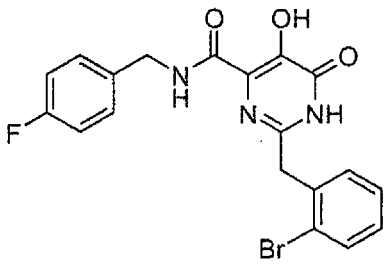
The compound was prepared according to the same procedure as in Example 21 using 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.08 g; 0.236 mmol) and isopropylamine (0.4 ml; 4.7 mmol). This gave the title compound as a white solid (0.021 g; 24%). LCMS: m/z = 367 (MH+).

Example 47: Preparation of 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid 4-chloro-benzylamide



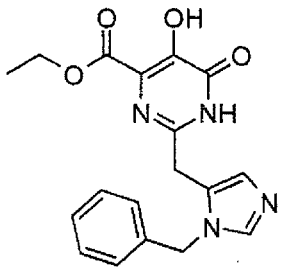
The compound was prepared according to the same procedure as in Example 21 using 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.08 g; 0.236 mmol) and 4-chlorobenzylamine (0.5 ml; 4.1 mmol). The title compound was prepared as a white solid (0.042 g; 39%). LCMS: m/z = 449 (MH+).

Example 48: Preparation of 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid 4-fluoro-benzylamide



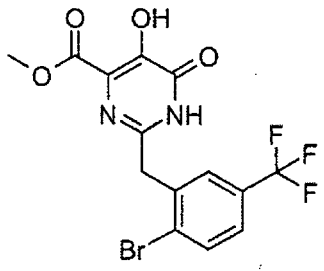
The compound was prepared according to the same procedure as in Example 21 using 2-(2-bromo-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.08 g; 0.236 mmol) and 4-fluorobenzylamine (0.5 ml; 4.4 mmol). This gave the title compound as a white solid (0.072 g; 70%). LCMS: m/z = 433 (MH+).

Example 49: Preparation of 2-(3-benzyl-3H-imidazol-4-ylmethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester



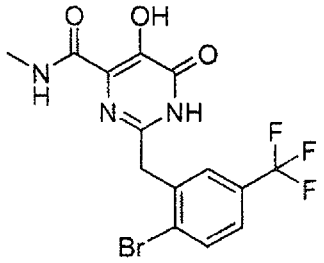
A solution of hydroxylamine hydrochloride (2.85 g, 41.1 mmol) in methanol (25 ml) and a solution of potassium hydroxide (2.3 g, 41.1 mmol) in methanol (25 ml) were combined at 0°C. The resulting salt was removed by filtration and the filtrate was immediately added to 2-(1-benzyl-1H-imidazol-5-yl)acetonitrile (1.62 g, 8.21 mmol). The resulting solution was heated at 60°C overnight and then evaporated to dryness. The residue was taken up into $CHCl_3$ (100 ml), and diethyl but-2-ynedioate (1.4 g, 8.21 mmol) was added. The resulting mixture was heated at 60°C overnight. After cooling, the crude reaction mixture was concentrated in vacuo. The residue was treated with water and EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was heated in xylene (2.5ml), at 140°C in a microwave reactor for 40 min. The cooled mixture was evaporated to dryness, dissolved in MeOH, passed through Celite® and then evaporated to dryness under reduced pressure. Purification by preparative HPLC provided the desired product as a yellow solid (0.014 g; 0.36%). LCMS: m/z = 355 (MH+) 75% purity.

Example 50: Preparation of 2-(2-bromo-5-trifluoromethyl-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



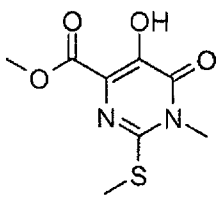
Preparation was performed following the general procedure used in Example 18 using 2-bromo-5-(trifluoromethyl)phenylacetonitrile (1 g; 3.78 mmol) and dimethyl but-2-ynedioate (1.09 g, 7.67 mmol) to provide the desired product as an off-white solid (0.29 g; 16%). LCMS: m/z = 408 (MH+).

Example 51: Preparation of 2-(2-bromo-5-trifluoromethyl-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



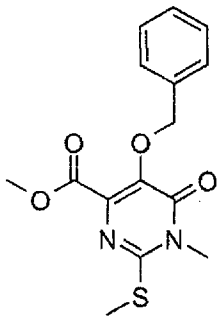
The compound was prepared according to the same procedure as in Example 21 using 2-(2-bromo-5-trifluoromethyl-benzyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester (0.080 g; 0.197 mmol) and 2M methylamine solution in THF (1 ml). This provided the title product as an off-white solid (0.043 g; 53%). LCMS: m/z = 427 (MH+).

Example 52: Preparation of 5-hydroxy-1-methyl-2-methylsulfanyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



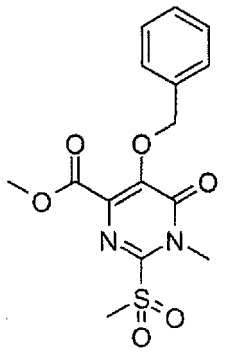
In a round-bottomed flask, thiocyanatomethane (17.5 g, 239 mmol) and N-methylhydroxylamine hydrochloride (20 g, 239 mmol) were combined with EtOH (100 ml) to give a light yellow solution. A solution of sodium carbonate (12.7 g, 120 mmol) in water (50 ml) was added slowly over 8 min at RT. The resulting mixture was stirred at RT for 2.5 days and then cooled in an ice bath. Dimethyl but-2-ynedioate (34.0 g, 239 mmol) was added slowly over 10 min and the resulting mixture was stirred for 2 hours, keeping the internal temperature below 22°C. Ice water and EtOAc were added. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resulting methyl 5-(2-methoxy-2-oxoethyl)-2-methyl-3-(methylthio)-2,5-dihydro-1,2,4-oxadiazole-5-carboxylate (62.7 g, 239 mmol) was placed in a round-bottomed flask, dissolved in xylene (110 ml), then heated at 140°C for 48 hours, cooled and then evaporated to dryness to give the crude title product as a brown solid. LCMS: m/z = 231 (MH+).

Example 53: Preparation 5-benzyloxy-1-methyl-2-methylsulfanyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



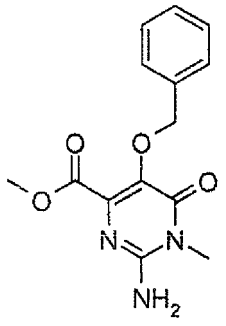
In a round-bottomed flask, methyl 5-hydroxy-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (55.0 g, 239 mmol) and potassium carbonate (33.0 g, 239 mmol) were combined with DMF (200 ml) to give a black suspension. Benzyl bromide (40.9 g, 239 mmol) was added and the resulting mixture was stirred at room temperature for 3.5 days. The reaction was quenched by the addition of cold water. The mixture was filtered to provide a brown solid. Chromatography (SiO_2; 10% to 50% EtOAc in hexanes) provided the desired product as an off-white solid (14.3 g; 18%). LCMS: m/z = 321 (MH+).

Example 54: Preparation 5-benzyloxy-2-methanesulfonyl-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



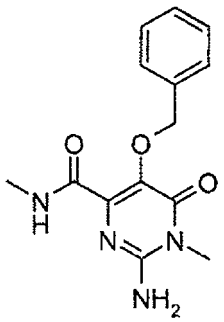
In a 1 L round-bottomed flask, methyl 5-(benzyloxy)-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (5.57 g, 17.4 mmol) was combined with MeOH (400 ml) and DCM (50 ml). A solution of oxone (21.4 g, 34.8 mmol) in water (100 ml) was added. The mixture was stirred at room temperature for 5 hours and then evaporated to dryness. The residue was taken up into EtOAc, washed with 3N NaOH aqueous solution, water, and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound as a white solid (3.7 g; 60%). LCMS: m/z = 353 (MH+).

Example 55: Preparation of 2-amino-5-benzyloxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester



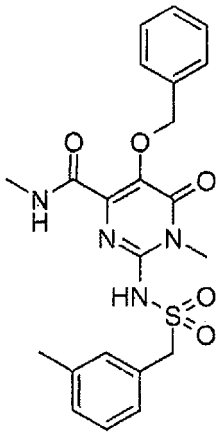
In a round-bottomed flask, methyl 5-(benzyloxy)-1-methyl-2-(methylsulfonyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (3.65 g, 10.4 mmol) was combined with CH_3CN (50 ml) to give a colorless solution. Gaseous ammonia was bubbled at 25°C for 20 min. The crude material was purified by flash chromatography (silica gel, 30% to 50% EtOAc in hexanes) and then through a second column (5% MeOH/DCM) to give the title product as a white solid. LCMS: m/z = 290 (MH+).

Example 56: Preparation of 2-amino-5-benzyloxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



To a mixture of methyl 2-amino-5-(benzyloxy)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (0.907 g, 3.14 mmol, Eq: 1.00), methylamine 2M in THF (12 ml, 24.0 mmol) was added. The mixture was heated in a microwave oven at 140°C for 2 h. The crude reaction mixture was concentrated in vacuo to give the title product as an off-white solid (0.90g; 100%). LCMS: m/z = 289 (MH+).

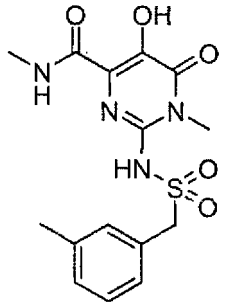
Example 57: Preparation of 5-benzyloxy-1-methyl-6-oxo-2-m-tolylmethanesulfonylamino-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



Potassium tert-butoxide (75.9 mg, 676 µmol) was added to a solution of 2-amino-5-(benzyloxy)-N,1-dimethyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (150 mg, 520 µmol) in THF (15.0 ml) and DMF (3 ml). The resulting mixture was stirred for 10 min and then cooled with an ice-bath. To this mixture was slowly added a solution of (3-methylphenyl)methanesulfonyl chloride (140 mg, 684 µmol) in THF (1 ml). The reaction

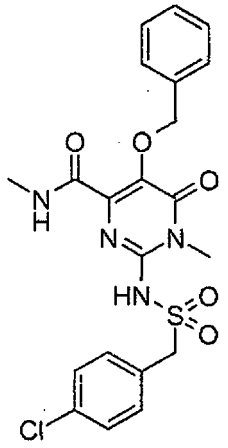
mixture was stirred at room temperature overnight. A further solution of (3-methylphenyl)methanesulfonyl chloride (140 mg, 684 µmol) in THF (1 ml) was added and then the mixture was stirred at room temperature for 48 hours. The resulting mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ aqueous solution and brine. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (silica gel, 0% to 2% MeOH in DCM) provided the desired product as a light yellow solid (0.070g; 29%). LCMS: m/z = 457 (MH+).

Example 58: Preparation of 5-hydroxy-1-methyl-6-oxo-2-m-tolylmethanesulfonylamino-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



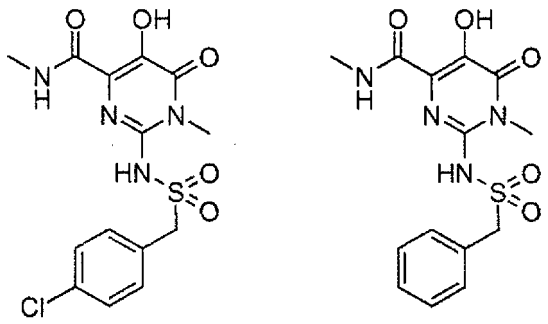
Palladium on carbon 10% (20 mg, 18.8 µmol) was added to a round-bottomed flask containing a solution of 5-(benzyloxy)-N,1-dimethyl-6-oxo-2-(m-tolylmethylsulfonamido)-1,6-dihydro-pyrimidine-4-carboxamide (0.07 g, 153 µmol) in ethyl acetate (5 ml) and MeOH (5 ml). The resulting mixture was degassed by nitrogen, evacuated and purged with hydrogen. The mixture was stirred at room temperature under an atmosphere of hydrogen for one hour, filtered and evaporated to dryness under reduced pressure. The residue was washed with hexane and DCM, and crystallized from MeOH/Et_2O to give the title compound as an off-white solid (0.03 g; 53%). LCMS m/z = 367 (MH+).

Example 59: Preparation of 5-benzyloxy-2-(4-chloro-phenylmethanesulfonylamino)-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



In a round-bottomed flask, 2-amino-5-(benzyloxy)-N,1-dimethyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (250 mg, 867 µmol, Eq: 1.00) was combined with THF (20 ml) to give a white suspension. DMF (4 ml) was added followed by potassium tert-butoxide (117 mg, 1.04 mmol, Eq: 1.2). The resulting mixture was stirred at room temperature for 10 min, then cooled with an ice bath. To this was slowly added a solution of (4-chlorophenyl)methanesulfonyl chloride (240 mg, 1.07 mmol, Eq: 1.23) in THF (1ml). After stirring at room temperature for 14 h, further t-BuOK (234 mgs) was added. The mixture was stirred for 5 min, cooled in the ice bath and then further (4-chlorophenyl)methanesulfonyl chloride (240 mg, 1.07 mmol) was added. The reaction mixture was stirred for 72 hours at RT and then diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine. Some solid precipitated in the EtOAc solution and was collected by filtration. The remaining filtrate was evaporated to dryness, purified by flash chromatography (silica gel, 2% to 6% MeOH in DCM) and then triturated by EtOAc/Hex. The solids were combined to give the desired product as a white solid (0.210 g; 51%). LCMS m/z = 477 (MH+).

Example 60: Preparation of 2-(4-chloro-phenylmethanesulfonylamino)-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide and 5-hydroxy-1-methyl-6-oxo-2-phenylmethanesulfonylamino-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide

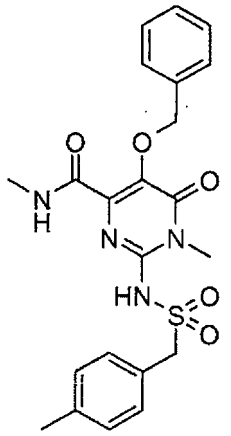


In a round-bottomed flask, 5-(benzyloxy)-2-((4-chlorophenyl)methylsulfonamido)-N,1-dimethyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (0.16 g, 335 µmol) was combined with ethyl acetate (40 ml) and MeOH (40.0 ml) to give a white suspension. Palladium on carbon 5% (50 mg, 470 µmol) was added and the solution was degassed by nitrogen. The mixture was stirred at room temperature under an atmosphere of hydrogen (balloon) for one hour and then the catalyst was removed by filtration and the filtrate was evaporated to dryness. Purification by preparative HPLC yielded:

2-(4-Chloro-phenylmethanesulfonylamino)-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide as a white amorphous solid (0.026 g; 20%). LCMS: m/z = 387 (MH+).

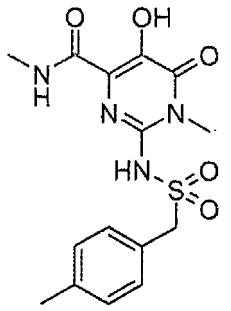
5-Hydroxy-1-methyl-6-oxo-2-phenylmethanesulfonylamino-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide as a white amorphous solid (0.022 g; 17%). LCMS: m/z = 353 (MH+).

Example 61: Preparation of 5-benzyloxy-1-methyl-6-oxo-2-p-tolylmethanesulfonyl-amino-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



Potassium tert-butoxide (93.8 mg, 836 µmol) was added to a solution of 2-amino-5-(benzyloxy)-N,1-dimethyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (110 mg, 380 µmol) **in THF (10 ml) in DMF (2 ml) [Comment: please check]**. After 10 min., the reaction mixture was cooled by an ice bath and then a solution of (4-methylphenyl)methanesulfonyl chloride (93.7 mg, 458 µmol) in THF (2 ml) was added. After 70 min., EtOAc and 1 N NaOH aqueous solution were added. The organic phase was extracted with EtOAc and then with DCM. The combined organic phases were washed with water, and brine, dried over Na_2SO_4 and evaporated to dryness. Chromatography (silica gel, 0 to 2% MeOH in DCM) provided the title compound as a pale yellow solid (0.080 g; 46%). LCMS: m/z = 457 (MH+).

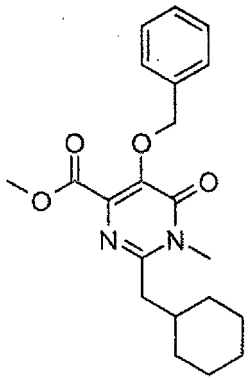
Example 62: Preparation of 5-hydroxy-1-methyl-6-oxo-2-p-tolylmethanesulfonylamino-1,6-dihydro-pyrimidine-4-carboxylic acid methylamide



A mixture of 5-(benzyloxy)-N,1-dimethyl-6-oxo-2-(p-tolylmethylsulfonamido)-1,6-dihydro-pyrimidine-4-carboxamide (80 mg, 175 µmol), palladium on carbon (186 mg, 87.6 µmol), MeOH (5 ml) and ethyl acetate (5 ml) was placed under an atmosphere of hydrogen. After stirring for 1.5 hour, the reaction mixture was filtered and evaporated to dryness.

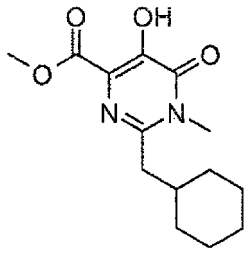
Crystallization from MeOH provided the title product as an off-white solid (0.045 g; 70%). LCMS: m/z = 367 (MH+).

Example 63: Preparation of 5-benzyloxy-2-cyclohexylmethyl-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid methyl ester



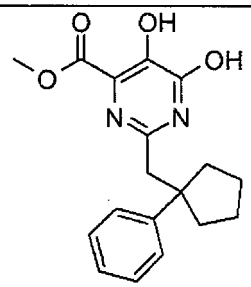
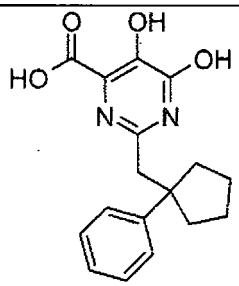
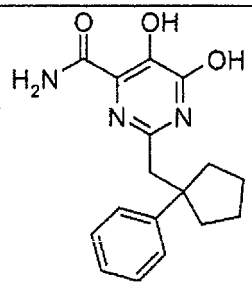
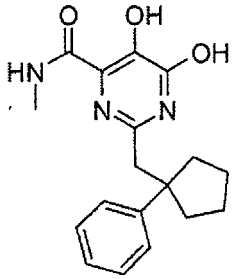
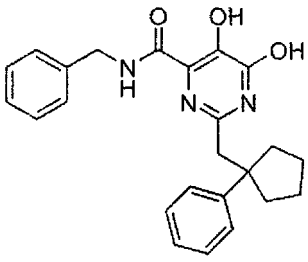
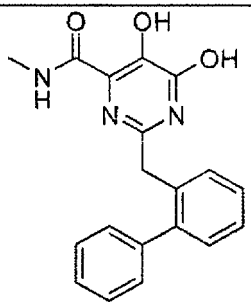
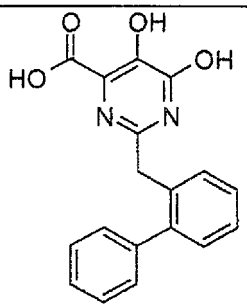
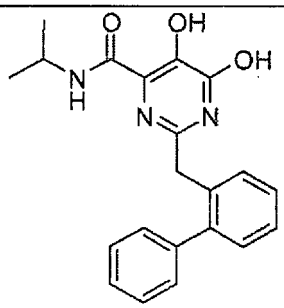
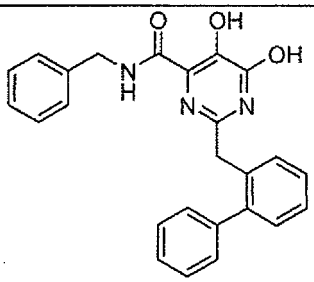
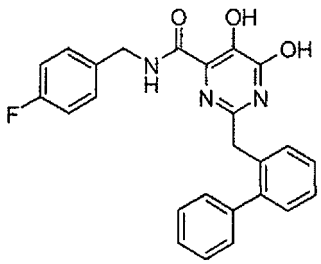
Cyclohexylmethylmagnesium bromide solution (1.77 ml; 885 µM of 0.5M solution in THF) was added dropwise to a solution of 5-benzyloxy-2-methanesulfonyl-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid methyl ester (0.26 g; 738 µM) in THF (10 ml). After stirring at room temperature for 1 h, the reaction mixture was quenched by the addition of saturated ammonium chloride solution. The product was extracted into EtOAc, washed with brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure to give the title product as a colourless oil (0.040 g; 70%). LCMS: m/z = 367 (MH+).

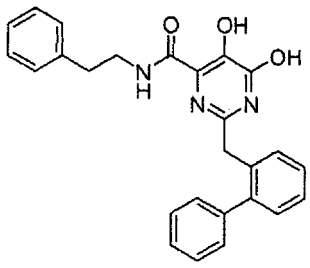
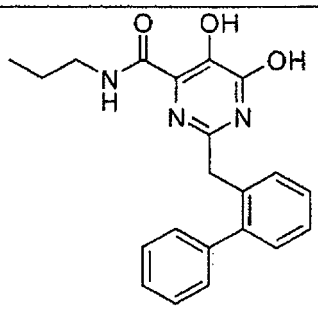
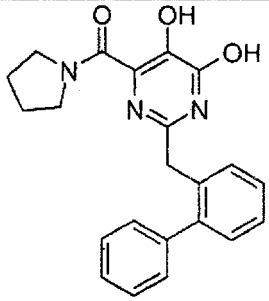
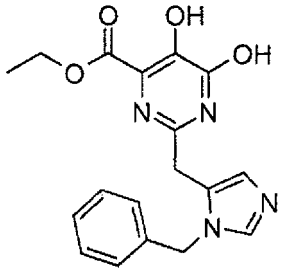
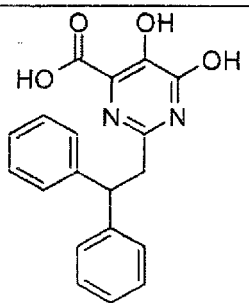
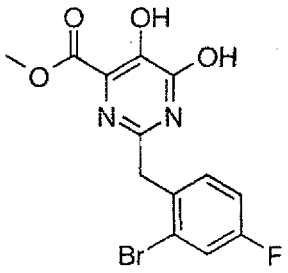
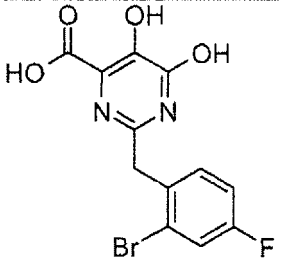
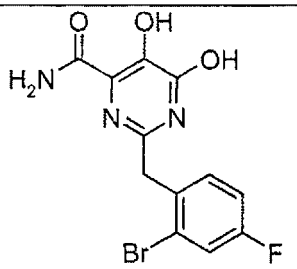
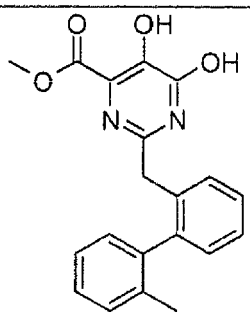
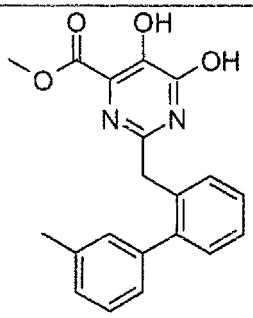
Example 64: Preparation of 2-cyclohexylmethyl-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid methyl ester

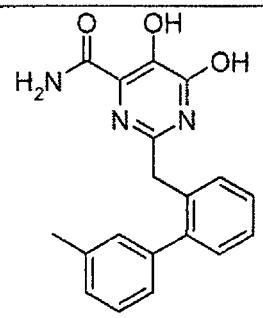
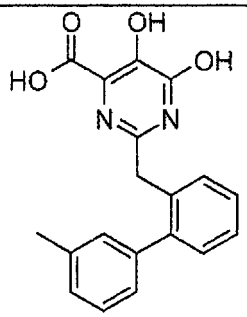
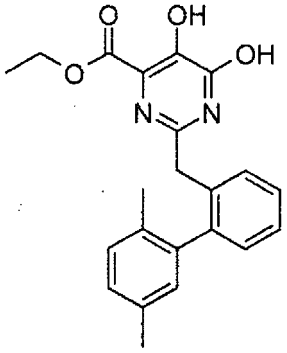
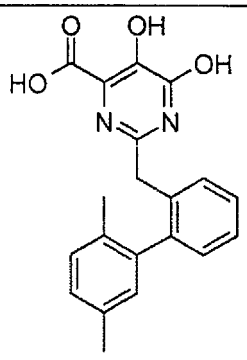
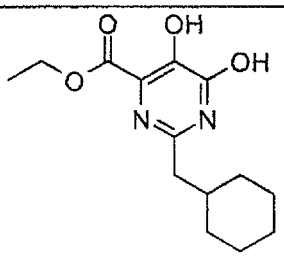
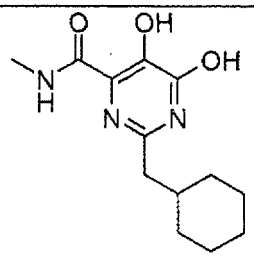
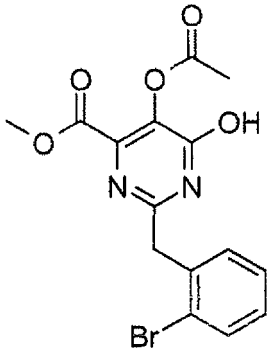
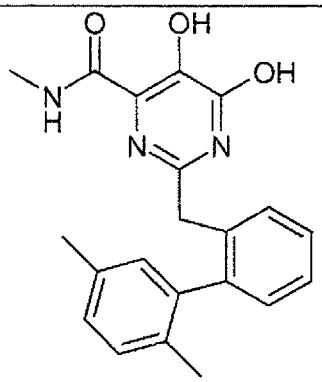
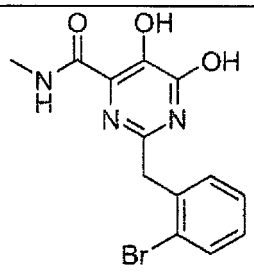
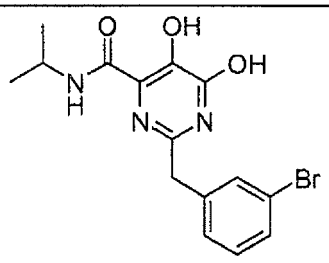


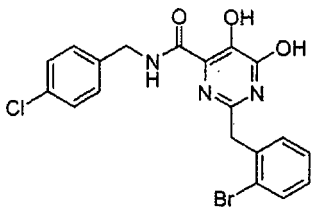
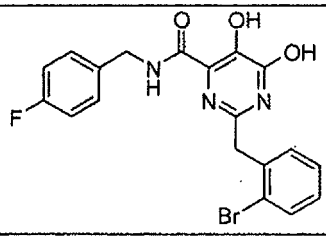
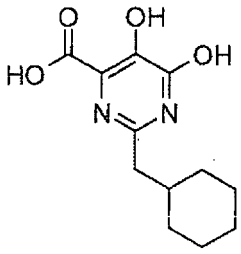
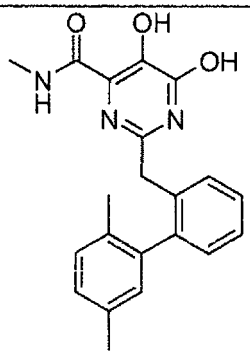
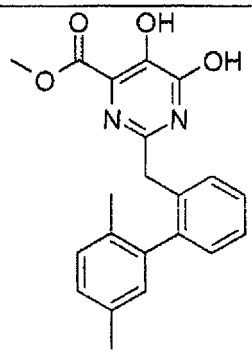
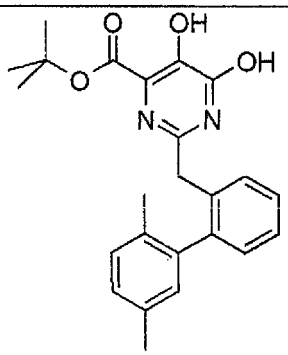
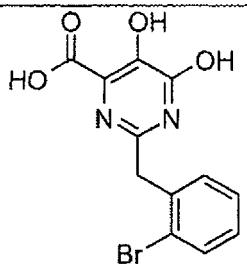
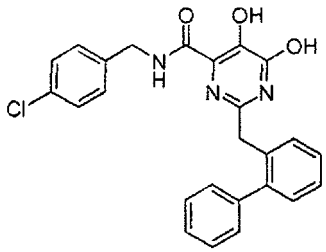
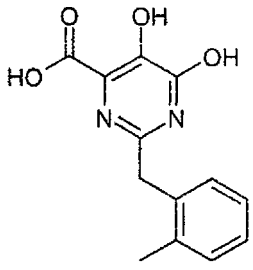
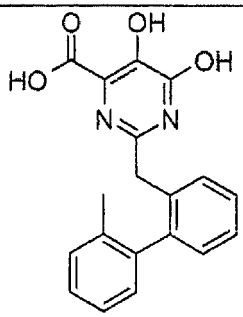
A mixture of methyl 5-(benzyloxy)-2-(cyclohexylmethyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (60 mg, 162 µmol) and 20% palladium hydroxide on carbon (11.4 mg, 16.2 µmol) in EtOAc (10 ml) was placed under an atmosphere of hydrogen and stirred at room temperature overnight. The mixture was filtered and then evaporated to dryness.

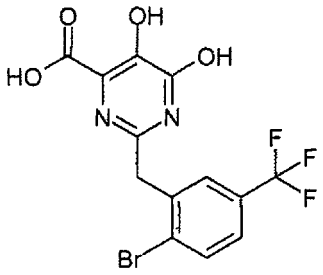
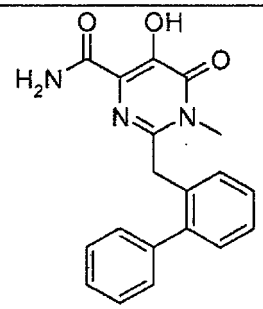
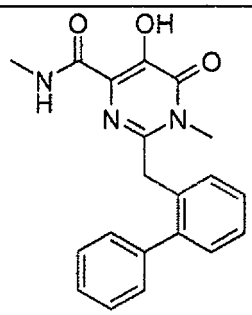
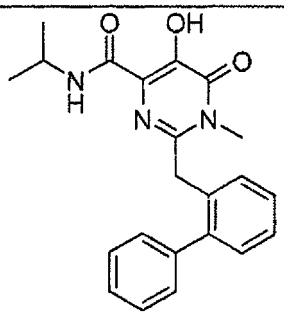
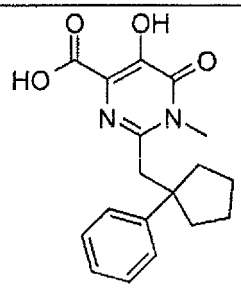
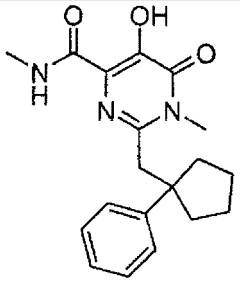
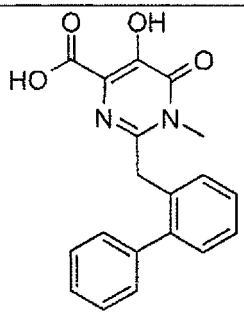
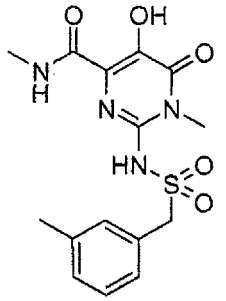
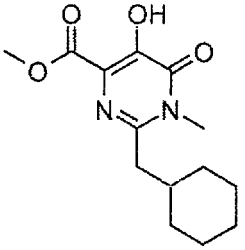
Chromatography (SiO_2; 0 to 20% EtOAc in hexanes) gave the title product as a white solid (0.032 g; 70%). LCMS: m/z = 281 (MH+).

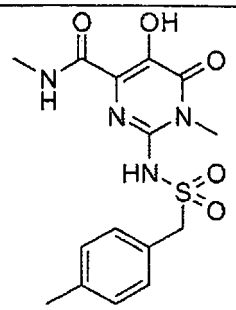
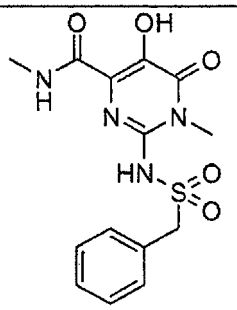
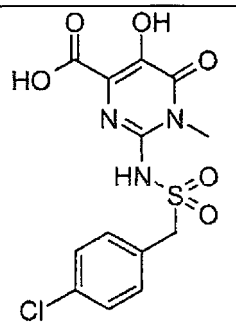
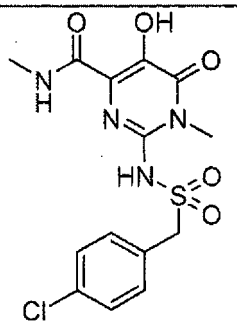
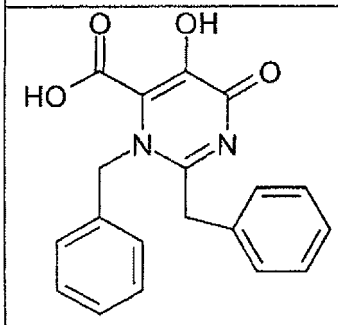
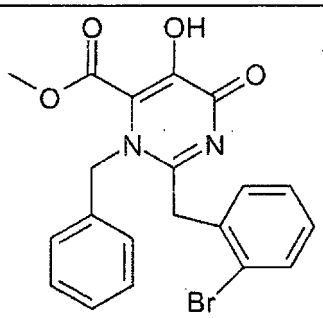
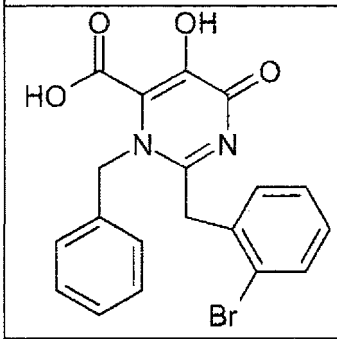
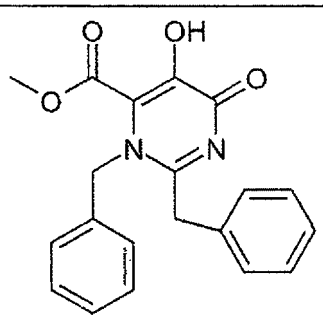
Structure	FRET	CPE	Structure	FRET	CPE
	IC_{50} = 0.41 µM	IC_{50} = 12 µM		IC_{50} = 0.08 µM	IC_{50} = 49 µM
	IC_{50} = 0.24 µM	IC_{50} = 42 µM		IC_{50} = 0.14 µM	IC_{50} = 22 µM
	IC_{50} = 1.1 µM	inactive		IC_{50} = 0.66 µM	inactive
	IC_{50} = 0.04 µM	inactive		IC_{50} = 8.2 µM	IC_{50} = 23 µM
	IC_{50} = 16 µM	inactive		IC_{50} = 1.7 µM	IC_{50} = 10 µM

	IC_{50} = 3.8 µM	IC_{50} = 8 µM		IC_{50} = 8.8 µM	not determ.
	IC_{50} = 1.1 µM	IC_{50} = 89 µM		IC_{50} = 9.5 µM	inactive
	IC_{50} = 2.5 µM	inactive		IC_{50} = 1.5 µM	inactive
	IC_{50} = 0.18 µM	inactive		IC_{50} = 2.7 µM	inactive
	IC_{50} = 0.12 µM	inactive		IC_{50} = 0.35 µM	not determ.

	IC_{50} = 0.55 µM	not determ.		IC_{50} = 0.23 µM	inactive
	IC_{50} = 0.22 µM	IC_{50} = 9.1 µM		IC_{50} = 0.03 µM	inactive
	IC_{50} = 3.2 µM	inactive		IC_{50} = 6.5 µM	inactive
	IC_{50} = 7.9 µM	inactive		IC_{50} = 0.53 µM	inactive
	IC_{50} = 5.7 µM	inactive		IC_{50} = 23 µM	not determ.

	37% @ 10 µM	inactive		IC_{50} = 27 µM	inactive
	IC_{50} = 0.21 µM	inactive		IC_{50} = 0.53 µM	inactive
	IC_{50} = 0.15 µM	IC_{50} = 16 µM		IC_{50} = 1.1 µM	IC_{50} = 11 µM
	IC_{50} = 0.25 µM	inactive		IC_{50} = 1.8 µM	inactive
	IC_{50} = 0.27 µM	inactive		IC_{50} = 0.24 µM	inactive

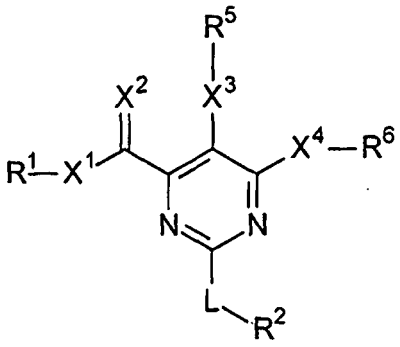
	IC_{50} = 0.16 µM	inactive		IC_{50} = 1.3 µM	inactive
	IC_{50} = 23 µM	inactive		IC_{50} = 14 µM	inactive
	IC_{50} = 0.26 µM	inactive		IC_{50} = 0.41 µM	IC_{50} = 11 µM
	IC_{50} = 1.3 µM	inactive		IC_{50} = 6.8 µM	inactive
				25% @ 10 µM	inactive

	IC_{50} = 13 µM	inactive		IC_{50} = 3 µM	inactive
	IC_{50} = 0.54 µM	inactive		IC_{50} = 5.8 µM	inactive
	IC_{50} = 3.8 µM	inactive		23% @ 10 µM	IC_{50} = 34 µM
	IC_{50} = 5.7 µM	inactive		IC_{50} = 19 µM	inactive

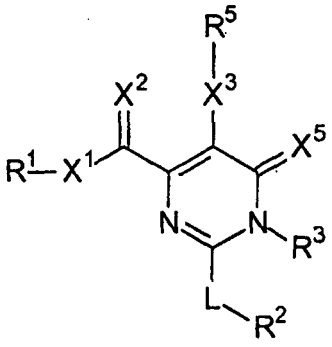
not determ. = not determined

CLAIMS

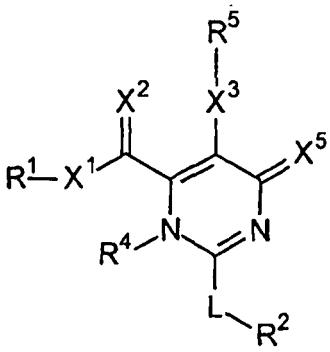
1. A compound having the general formula (Di), (Dii), or (Diii), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(Di)



(Dii)



(Diii)

wherein

X^1 is O, S or NR*;

X^2 is O or S;

X^3 is O or S;

X^4 is O or S;

X^5 is O or S;

L is $-(CH_2)_m-$, $-NR^*-SO_2-$ or $-SO_2-NR^*-$;

m is 1 to 4;

R^1 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted aryl), –C(O)–O–R** or $-P(O)(OR^{**})_2$, if X^1 is NR* then R^1 and R* can optionally be bound together to form a 5- to 7-membered ring;

R^2 is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring, wherein the hydrocarbon group can be optionally substituted;

R^3 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or –C_{1-4} alkyl–(optionally substituted aryl);

R^4 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or –C_{1-4} alkyl–(optionally substituted aryl);

R^5 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl);

R^6 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl);

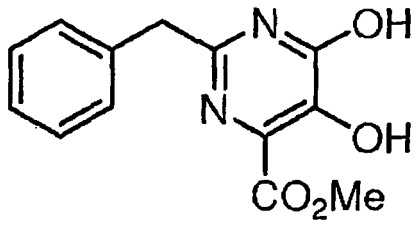
R* is –H, or –(C_{1-6} alkyl); and

R** is –H, –(C_{1-6} alkyl), –(C_{3-7} cycloalkyl), –(aryl), or –C_{1-4} alkyl–(aryl);

wherein the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, –NR*R*, –OH, and –O–C_{1-6} alkyl; and

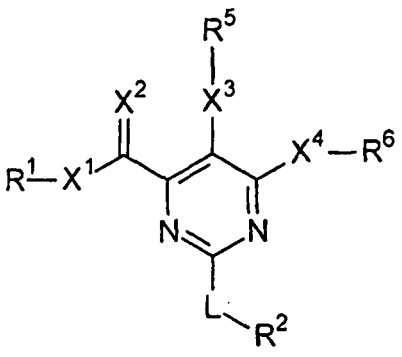
wherein the optional substituent of the cycloalkyl group, the aryl group or the hydrocarbon group is selected from the group consisting of –C_{1-6} alkyl, –halogen, –CF_3, –CN, –X^1–R*, –aryl and –C_{1-4} alkyl–aryl,

with the proviso that the following compound

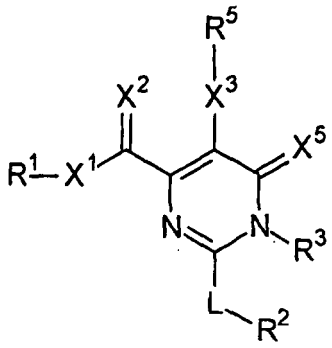


is disclaimed.

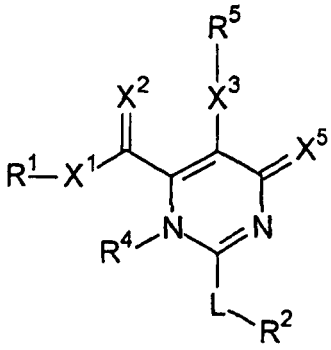
2. A pharmaceutical composition comprising a compound having the general formula (Di), (Dii), or (Diii), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(Di)



(Dii)



(Diii)

wherein

X^1 is O, S or NR*;

X^2 is O or S;

X^3 is O or S;

X^4 is O or S;

X^5 is O or S;

L is $-(CH_2)_m-$, $-NR^*-SO_2-$ or $-SO_2-NR^*-$;

m is 1 to 4;

R^1 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted aryl), –C(O)–O–R** or $-P(O)(OR^{**})_2$, if X^1 is NR* then R^1 and R* can optionally be bound together to form a 5- to 7-membered ring;

R^2 is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring, wherein the hydrocarbon group can be optionally substituted;

R^3 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or $-C_{1-4}$ alkyl–(optionally substituted aryl);

R^4 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or $-C_{1-4}$ alkyl–(optionally substituted aryl);

R^5 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl);

R^6 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl);

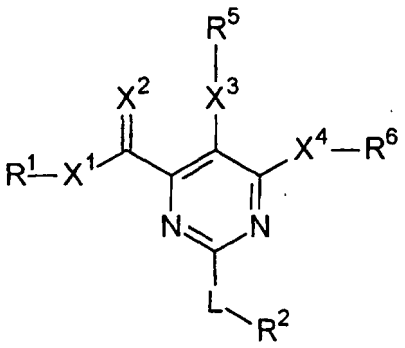
R* is –H, or $-(C_{1-6}$ alkyl); and

R** is –H, $-(C_{1-6}$ alkyl), $-(C_{3-7}$ cycloalkyl), –(aryl), or $-C_{1-4}$ alkyl–(aryl);

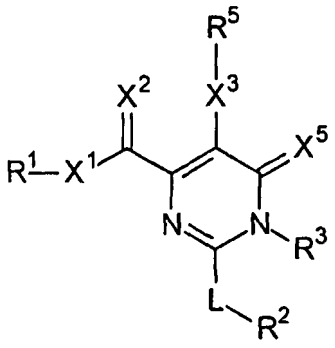
wherein the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, –NR*R*, –OH, and –O–C_{1-6} alkyl; and
wherein the optional substituent of the cycloalkyl group, the aryl group or the hydrocarbon group is selected from the group consisting of –C_{1-6} alkyl, –halogen, –CF_3, –CN, –X^1–R*, –aryl and –C_{1-4} alkyl–aryl,

and optionally a pharmaceutically acceptable excipient.

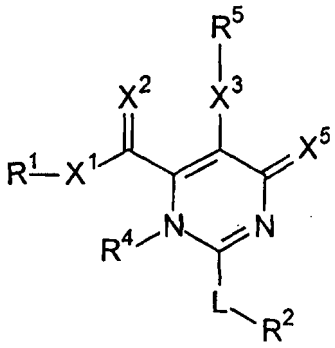
3. A compound having the general formula (Di), (Dii), or (Diii), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(Di)



(Dii)



(Diii)

wherein

X^1 is O, S or NR*;

X^2 is O or S;

X^3 is O or S;

X^4 is O or S;

X^5 is O or S;

L is –$(CH_2)_m$–, –NR*–SO_2– or –SO_2–NR*–;

m is 1 to 4;

R^1 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), –C_{1-4} alkyl–(optionally substituted aryl), –C(O)–O–R** or –P(O)$(OR^{**})_2$, if X^1 is NR* then R^1 and R* can optionally be bound together to form a 5- to 7-membered ring;

R^2 is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring, wherein the hydrocarbon group can be optionally substituted;

R^3 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or –C_{1-4} alkyl–(optionally substituted aryl);

R^4 is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or –C_{1-4} alkyl–(optionally substituted aryl);

R^5 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl);

R^6 is –H, –C(O)–(optionally substituted C_{1-6} alkyl), or –(optionally substituted C_{1-6} alkyl);

R* is –H, or –(C_{1-6} alkyl); and

R** is –H, –(C_{1-6} alkyl), –(C_{3-7} cycloalkyl), –(aryl), or –C_{1-4} alkyl–(aryl);

wherein the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, –NR*R*, –OH, and –O–C_{1-6} alkyl; and
wherein the optional substituent of the cycloalkyl group, the aryl group or the hydrocarbon group is selected from the group consisting of –C_{1-6} alkyl, –halogen, –CF_3, –CN, –X^1–R*, –aryl and –C_{1-4} alkyl–aryl,

wherein the compound is for use in the treatment, amelioration or prevention of a viral disease.

4. The compound according to claim 3, wherein the viral disease is caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae.

5. The compound according to claim 4, wherein the viral disease is influenza.

6. A method of treating, ameliorating or preventing a viral disease, the method comprising administering to a patient in need thereof an effective amount of a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.

7. The method according to claim 6, wherein the viral disease is caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae.

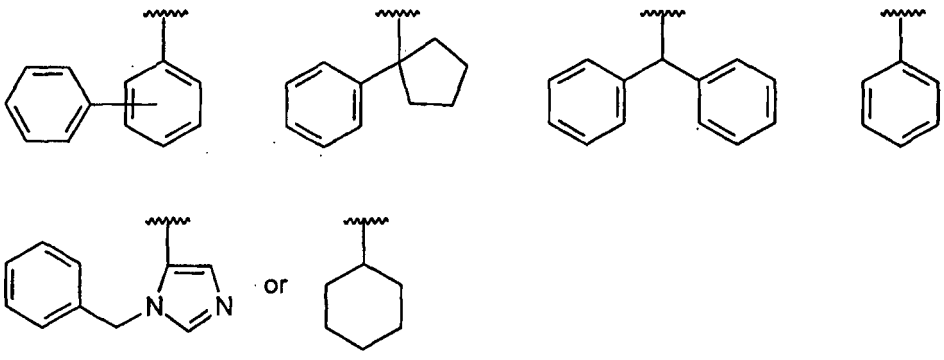
8. The method according to claim 7, wherein the viral disease is influenza.

9. The compound according to claim 1, 3, 4, or 5, the pharmaceutical composition according to claim 2, or the method according to claim 6, 7, or 8, wherein m is 1 or 2.

10. The compound according to claim 1, 3, 4, or 5, the pharmaceutical composition according to claim 2, or the method according to claim 6, 7, or 8, wherein R^1 is –H or –(optionally substituted C_{1-6} alkyl).

11. The compound according to claim 1, 3, 4, or 5, the pharmaceutical composition according to claim 2, or the method according to claim 6, 7, or 8, wherein R^2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted C_{5-7} cycloalkyl.

12. The compound according to claim 1, 3, 4, or 5, the pharmaceutical composition according to claim 2, or the method according to claim 6, 7, or 8, wherein R^2 is



and wherein the heterocyclic group, phenyl group, cyclohexyl group or cyclopentyl group can be optionally substituted in any available position by a substituent which is independently selected from $-C_{1-6}$ alkyl, halogen, $-CF_3$, –CN, –OH, and $-O-C_{1-6}$ alkyl.

13. The compound according to claim 1, 3, 4, or 5, the pharmaceutical composition according to claim 2, or the method according to claim 6, 7, or 8, wherein L is $-(CH_2)_m-$, or $-NR^*-SO_2-$.

14. The compound according to claim 1, 3, 4, or 5, the pharmaceutical composition according to claim 2, or the method according to claim 6, 7, or 8, wherein X^1 is O or NR*.

15. The compound according to claim 3, or the method according to claim 6, wherein a further antiviral agent is to be administered concurrently or sequentially with the compound according to claim 3.

16. A pharmaceutical composition comprising:

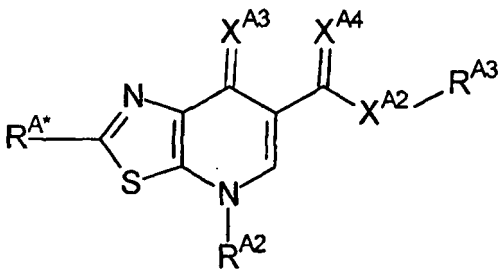
(i) a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3; and

(ii) at least one polymerase inhibitor which is different from the compound having the general formula (Di), (Dii), or (Diii);

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

17. The pharmaceutical composition according to claim 16, wherein the at least one polymerase inhibitor which is different from the compound having the general formula (Di), (Dii), or (Diii) is selected from

(a) a compound having the general formula (A), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(A)

wherein

R^{A*} is –H, –Hal, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), $–C_{1-4}$ alkyl–(optionally substituted aryl) or $–X^1–R^1$;

X^{A1} is O, C(O), C(O)O, OC(O); S, SO, SO_2, NR^{A4}, $N(R^{A5})C(O)$, $C(O)NR^{A5}$;

X^{A2} is O, S, NR^{A4};

X^{A3} is O or S;

X^{A4} is O or S;

R^{A1} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), $–C_{1-4}$ alkyl–(optionally substituted aryl);

R^{A2} is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring, wherein the hydrocarbon group can be optionally substituted;

R^{A3} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), or $–C_{1-4}$ alkyl–(optionally substituted aryl) if X^{A2} is NR^{A4} then R^{A3} can also be –OH;

R^{A4} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $–C_{1-4}$ alkyl–(optionally substituted aryl) or if X^{A1} is NR^{A4}, then R^{A4} and R^{A1} can be joined together to form a 5- to 7-membered ring, which can optionally contain O, S or further N or if X^{A2} is NR^{A4}, then R^{A4} and R^{A3} can be joined together to form a 5- to 7-membered ring, which can optionally contain O, S or further N; and

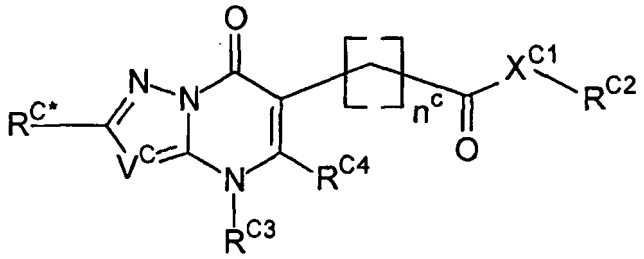
R^{A5} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $–C_{1-4}$ alkyl–(optionally substituted aryl); and

R^{A6} is –H, or $–C_{1-6}$ alkyl;

wherein the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, $–NR^{A6}R^{A6}$, –OH, and $–O–C_{1-6}$ alkyl;

wherein the optional substituent of the cycloalkyl group, the aryl group or the hydrocarbon group is selected from the group consisting of $–C_{1-6}$ alkyl, halogen, $–CF_3$, –CN, $–X^{A1}–R^{A5}$ and $–C_{1-4}$ alkyl–aryl; and

(b) a compound having the general formula (C), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(C)

wherein

V^C is N, or CR^{C6};

X^{C1} is O, S, or NR^{C8};

X^{C2} is NR^{C5}, $N(R^{C5})C(O)$, $C(O)NR^{C5}$, O, C(O), C(O)O, OC(O); S, SO, SO_2, $SO_2N(R^{C5})$ or $N(R^{C5})SO_2$;

R^{C*} is –H, –Hal, –(optionally substituted C_{1-6} alkyl), –(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S), $–C_{1-4}$ alkyl–(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S), or $–X^{C2}–R^{C1}$;

R^{C1} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S), $–C_{1-4}$ alkyl–(optionally substituted mono- or polycyclic group containing 3 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S);

R^{C2} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $–C_{1-4}$ alkyl–(optionally substituted aryl) or if X^{C1} is $NR^{C'}$, then R^{C2} can also be –OH;

R^{C3} is –H, $–R^{C7}$, or $–X^{C2}–R^{C7}$;

R^{C4} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $–C_{1-4}$ alkyl–(optionally substituted aryl);

R^{C5} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $–C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $–C_{1-4}$ alkyl–(optionally substituted aryl);

R^{C6} H, $–C_{1-6}$ alkyl, –aryl, halogen or CN;

R^{C7} is –(optionally substituted hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring);

R^{C8} is –H, or $–C_{1-6}$ alkyl; and

n^C is 0 to 4;

wherein the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, $–NR^{C5}R^{C5}$, –OH, and $–O–C_{1-6}$ alkyl;
wherein the optional substituent of the cycloalkyl group, the aryl group, the mono- or polycyclic group or the hydrocarbon group is selected from the group consisting of $–C_{1-6}$ alkyl, halogen, $-CF_3$, –CN, $–X^{C2}–R^{C8}$ and $–C_{1-4}$ alkyl–aryl;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

18. A pharmaceutical composition comprising:

(i) a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3; and

(ii) at least one neuramidase inhibitor;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

19. A pharmaceutical composition comprising:

(i) a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3; and

(ii) at least one M2 channel inhibitor;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

20. A pharmaceutical composition comprising:

(i) a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3; and

(ii) at least one alpha glucosidase inhibitor;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

21. A pharmaceutical composition comprising:

(i) a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3; and

(ii) at least one ligand of another influenza target;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

22. A pharmaceutical composition comprising:

(i) a compound having the general formula (Di), (Dii), or (Diii) as defined in claim 3; and

(ii) at least one medicament selected from antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

23. The pharmaceutical composition as defined in any of claims 16 to 22 for use in the treatment, amelioration or prevention of a viral disease.

24. A method of treating, ameliorating or preventing a viral disease, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition as defined in any of claims 16 to 22.

25. The pharmaceutical composition according to claim 23 or the method according to claim 24, wherein the viral disease is caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae; more specifically wherein the viral disease is influenza.

26. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein the compound having the general formula (Di), (Dii), or (Diii) exhibits a % reduction of at least about 30 % at 50 μM in the CPE assay disclosed herein.

27. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein the compound having the general formula (Di), (Dii), or (Diii) exhibits an IC_{50} of at least about 40 μM in the FRET endonuclease activity assay disclosed herein.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/066388

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/06 C07D239/52 C07D239/557 A61K31/505 A61K31/506
A61K31/513 A61P31/12 A61P31/14 A61P31/16 A61P31/20
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/035076 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; DI FRANCESCO MARIA EMILIA [IT]; GA) 1 May 2003 (2003-05-01)	1-4,9, 11-15, 23,25
Y	abstract	16-22,
	pages 98, 126	26,27
A	page 135	5,10
	pages 183-194; table 10	
	pages 65-66	
	pages 75-80	
	claims 1-50	

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2014	23/01/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dunet, Guillaume

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	WO 03/035077 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; CRESCENZI BENEDETTA [IT]; GARDELLI) 1 May 2003 (2003-05-01) abstract pages 55-56 pages 64-69 pages 107-108 pages 145-150 claims 1-28	1-4,9, 11-15, 23,25 16-22, 26,27 5,10

X	WO 2012/088283 A1 (BAYLOR COLLEGE MEDICINE [US]; HORTON LORI [US]; PALZKILL TIMOTHY [US];) 28 June 2012 (2012-06-28) abstract paragraph [0116] claims 1-47	1,2,9-15

X	EP 1 698 628 A1 (SHIONOGI & CO [JP]) 6 September 2006 (2006-09-06) abstract page 28; compound 3 claims 1-22	1,9-14

X	CN 102 617 487 A (UNIV BEIJING TECHNOLOGY) 1 August 2012 (2012-08-01) claims 1-10 page 8; compound IV page 9; compound VI paragraphs [0060], [0067], [0073], [0113] paragraphs [0120], [0126], [0155], [0161], [0167] paragraphs [0197], [0203], [0208], [0236] paragraphs [0242], [0247], [0319], [0325]	1,9-14

Y A	WO 2005/070901 A2 (GILEAD SCIENCES INC [US]; JIN HAOLUN [US]; KIM CHOUNG U [US]) 4 August 2005 (2005-08-04) abstract page 57 pages 61-62 pages 70, 74 pages 90-91 pages 140-150 claims 1-46	16-22 1-5, 9-15,23, 25-27

A	WO 2011/046920 A1 (BAYLOR COLLEGE MEDICINE [US]; SONG YONGCHENG [US]) 21 April 2011 (2011-04-21) abstract page 65; compound 30 claims 1-13	1-5, 9-23,25, 27

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1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. HISAKI ET AL: "Synthesis and anti-influenza virus activity of novel pyrimidine derivatives", ANTIVIRAL RESEARCH, vol. 42, no. 2, June 1999 (1999-06), pages 121-137, XP55080864, ISSN: 0166-3542, DOI: 10.1016/S0166-3542(99)00019-4 abstract tables 1-7 page 135, paragraph 4.	5
X,P	WO 2012/151567 A1 (ST JUDE CHILDRENS RES HOSPITAL; WEBB THOMAS R [US]; BOYD VINCENT A [US) 8 November 2012 (2012-11-08) abstract * compounds *; pages 66-423 pages 425-426; table 2 claims 1-15	1-5, 9-23, 25-27
X,P	CN 102 911 124 A (UNIV SHANDONG) 6 February 2013 (2013-02-06) abstract claims 1-8 pages 25-26; compound 5o	1-4,9, 11-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/066388

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6-8, 24(completely); 9-15, 25-27(partially)
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 6-8 and 24 as well as claims 9-15 and 25-27 partially are directed towards methods of treatment of the human body by therapy and fall therefore under the provisions of Rules 39.1(iv) PCT and 67.1(iv) PCT.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/066388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03035076 A1	01-05-2003	AT 355064 T	15-03-2006
		CA 2463975 A1	01-05-2003
		DE 60218511 T2	25-10-2007
		DK 1441734 T3	11-06-2007
		EP 1441734 A1	04-08-2004
		ES 2281565 T3	01-10-2007
		JP 4351053 B2	28-10-2009
		JP 2005510500 A	21-04-2005
		PT 1441734 E	31-05-2007
		SI 1441734 T1	31-08-2007
		US 2005075356 A1	07-04-2005
		US 2007083045 A1	12-04-2007
		WO 03035076 A1	01-05-2003
WO 03035077 A1	01-05-2003	AT 318140 T	15-03-2006
		AU 2002334207 B2	23-02-2006
		BR 0213522 A	08-09-2004
		CA 2463976 A1	01-05-2003
		CN 102219750 A	19-10-2011
		CN 102229605 A	02-11-2011
		CO 5580777 A2	30-11-2005
		DE 60209381 T2	05-10-2006
		DE 122008000016 I1	01-12-2011
		DE 122009000048 I1	08-04-2010
		DK 1441735 T3	12-06-2006
		EP 1441735 A1	04-08-2004
		ES 2258668 T3	01-09-2006
		GE P20063848 B	12-06-2006
		HK 1085665 A1	25-11-2011
		HR P20040373 A2	31-08-2005
		HU 0401740 A2	28-12-2004
		IL 161337 A	17-02-2010
		IS 7213 A	07-04-2004
		JP 3927175 B2	06-06-2007
		JP 2005511543 A	28-04-2005
		LU 91428 I2	09-06-2008
		MX PA04003932 A	18-06-2004
		NL 300340 I1	02-06-2008
		NO 325206 B1	25-02-2008
		NO 2008007 I1	23-06-2008
		NZ 533057 A	25-11-2005
		PL 212914 B1	31-12-2012
		PT 1441735 E	30-06-2006
		RS 51542 B	30-06-2011
		SI 1441735 T1	30-06-2006
		US 2005025774 A1	03-02-2005
		US 2006258860 A1	16-11-2006
		US 2007123524 A1	31-05-2007
		US 2008275004 A1	06-11-2008
		US 2011034449 A1	10-02-2011
		WO 03035077 A1	01-05-2003
		YU P35604 A	17-08-2006
WO 2012088283 A1	28-06-2012	US 2012329842 A1	27-12-2012
		WO 2012088283 A1	28-06-2012
EP 1698628 A1	06-09-2006	EP 1698628 A1	06-09-2006
		JP 4798608 B2	19-10-2011

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/066388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2007149556 A1	28-06-2007
		US 2010204237 A1	12-08-2010
		WO 2005061490 A1	07-07-2005
CN 102617487 A	01-08-2012	NONE	
WO 2005070901 A2	04-08-2005	AU 2005206511 A1	04-08-2005
		BR PI0506786 A	22-05-2007
		CA 2552584 A1	04-08-2005
		CN 1934093 A	21-03-2007
		EP 1711476 A2	18-10-2006
		JP 2007517900 A	05-07-2007
		KR 20060124701 A	05-12-2006
		US 2005282839 A1	22-12-2005
		WO 2005070901 A2	04-08-2005
WO 2011046920 A1	21-04-2011	US 2013065857 A1	14-03-2013
		WO 2011046920 A1	21-04-2011
WO 2012151567 A1	08-11-2012	NONE	
CN 102911124 A	06-02-2013	NONE	

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104619699 A
(43)申请公布日 2015.05.13

(21)申请号 201380041462.1
(22)申请日 2013.08.05
(30)优先权数据
61/679,968 2012.08.06 US
(85)PCT国际申请进入国家阶段日
2015.02.04
(86)PCT国际申请的申请数据
PCT/EP2013/066388 2013.08.05
(87)PCT国际申请的公布数据
WO2014/023691 EN 2014.02.13
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(51)Int.Cl.
C07D 403/06(2006.01)
C07D 239/52(2006.01)
C07D 239/557(2006.01)
A61K 31/505(2006.01)
A61K 31/506(2006.01)
A61K 31/513(2006.01)
A61P 31/12(2006.01)
A61P 31/14(2006.01)
A61P 31/16(2006.01)
A61P 31/20(2006.01)

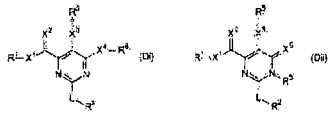
权利要求书8页 说明书55页

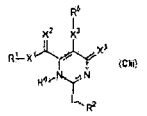
(54)发明名称

二羟基嘧啶碳酸衍生物以及它们在治疗、改善或预防病毒疾病中的用途

(57)摘要

本发明涉及可用于治疗、改善或预防病毒疾病的通式(Di)、(Dii)或(Diii)的化合物，其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。

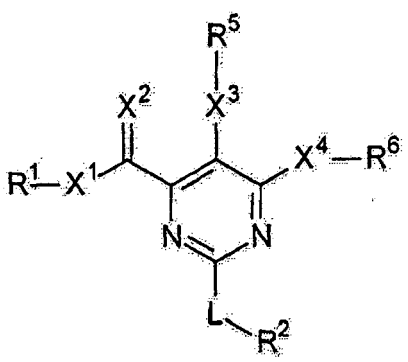




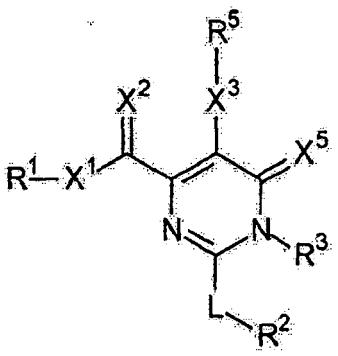
此外，还公开了具体的组合疗法。

CN 104619699 A

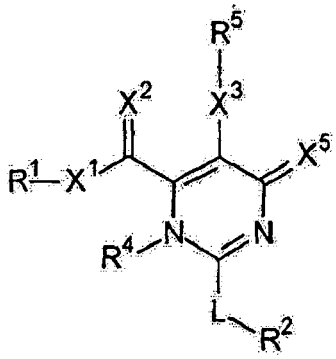
1. 通式 (Di)、(Dii) 或 (Diii) 的化合物，其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式，



(Di)



(Dii)



(Diii)

其中

X^1是 O、S 或 NR*；

X^2是 O 或 S；

X^3是 O 或 S；

X^4是 O 或 S；

X^5是 O 或 S；

L 是 $-(CH_2)_m-$、$-NR*-SO_2-$ 或 $-SO_2-NR*-$；

m 是 1-4；

R^1是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、$-C_{1-4}$烷基 -（任选被取代的芳基）、-C(O)-O-R** 或 -P(O)(OR**)$_2$，如果 X^1是 NR*，则 R^1和 R* 可以任选地结合在一起形成 5 — 7 元环；

R^2是含有 5-20 个碳原子并且任选含有 1-4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基，其中所述烃基可以任选被取代；

R^3是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 $-C_{1-4}$烷基 -（任选被取代的芳基）；

R^4是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 $-C_{1-4}$烷基 -（任选被取代的芳基）；

R^5是 -H、-C(O)-（任选被取代的 C_{1-6}烷基）或 -（任选被取代的 C_{1-6}烷基）；

R^6是 -H、-C(O)-（任选被取代的 C_{1-6}烷基）或 -（任选被取代的 C_{1-6}烷基）；

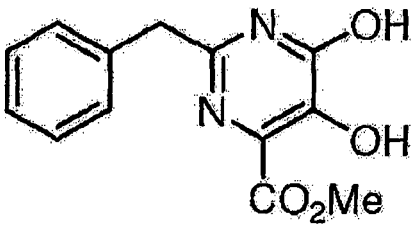
R* 是 -H 或 -（C_{1-6}烷基）；且

R** 是 -H、-（C_{1-6}烷基）、-（C_{3-7}环烷基）、-（芳基）或 $-C_{1-4}$烷基 -（芳基）；

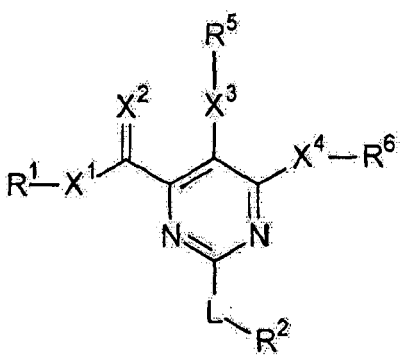
其中所述的烷基的任选的取代基选自卤素、-CN、-NR*R*、-OH 和 -O-C_{1-6}烷基；且

其中所述的环烷基、芳基或烃基的任选的取代基选自 $-C_{1-6}$烷基、- 卤素、$-CF_3$、-CN、$-X^1-R*$、- 芳基和 $-C_{1-4}$烷基 - 芳基，

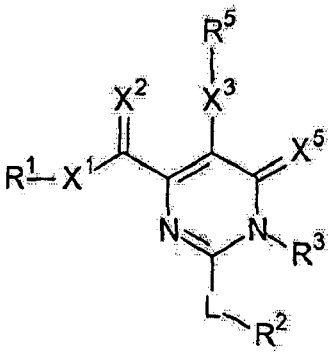
条件是不包括下面的化合物：



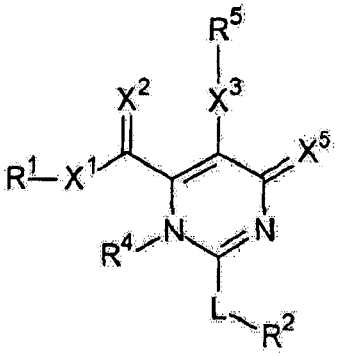
2. 药物组合物，其包含通式 (Di)、(Dii) 或 (Diii) 的化合物，并且任选包含药学上可接受的赋形剂，所述通式 (Di)、(Dii) 或 (Diii) 的化合物任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式，



(Di)



(Dii)



(Diii)

其中

X^1是 O、S 或 NR*；

X^2是 O 或 S；

X^3是 O 或 S；

X^4是 O 或 S；

X^5是 O 或 S；

L 是 $-(CH_2)_m-$、-NR*-SO_2- 或 -SO_2-NR*-；

m 是 1-4；

R^1是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的芳基）、-C(O)-O-R** 或 -P(O)$(OR^{**})_2$，如果 X^1是 NR*，则 R^1和 R* 可以任选地结合在一起形成 5 — 7 元环；

R^2是含有 5 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基，其中所述烃基可以任选被取代；

R^3是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 -C_{1-4}烷基 -（任选被取代的芳基）；

R^4是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 -C_{1-4}烷基 -（任选被取代的芳基）；

R^5是 -H、-C(O)-（任选被取代的 C_{1-6}烷基）或 -（任选被取代的 C_{1-6}烷基）；

R^6是 -H、-C(O)-（任选被取代的 C_{1-6}烷基）或 -（任选被取代的 C_{1-6}烷基）；

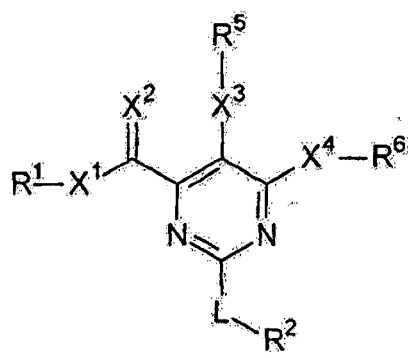
R* 是 -H 或 -(C_{1-6}烷基）；且

R** 是 -H、-(C_{1-6}烷基）、-(C_{3-7}环烷基）、-（芳基）或 -C_{1-4}烷基 -（芳基）；

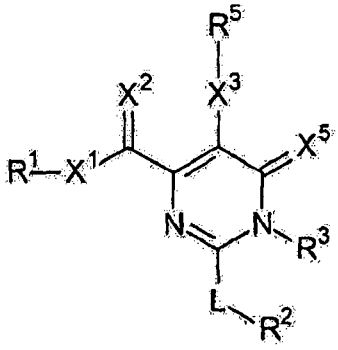
其中所述的烷基的任选的取代基选自卤素、-CN、-NR*R*、-OH 和 -O-C_{1-6}烷基；且

其中所述的环烷基、芳基或烃基的任选的取代基选自 -C_{1-6}烷基、- 卤素、-CF_3、-CN、-X^1-R*、- 芳基和 -C_{1-4}烷基 - 芳基。

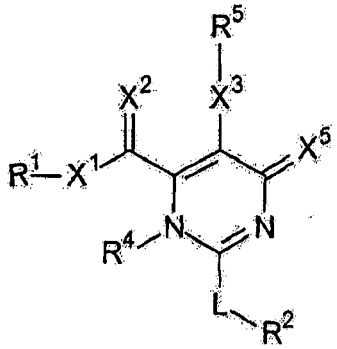
3. 通式 (Di)、(Dii) 或 (Diii) 的化合物，其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式，



(Di)



(Dii)



(Diii)

其中

X^1是 O、S 或 NR*；

X^2是 O 或 S；

X^3是 O 或 S；

X^4是 O 或 S；

X^5是 O 或 S；

L 是 -$(CH_2)_m$-、-NR*-SO_2- 或 -SO_2-NR*-；

m 是 1-4；

R^1是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的芳基）、-C(O)-O-R** 或 -P(O)(OR**)$_2$，如果X^1是 NR*，则R^1和 R* 可以任选地结合在一起形成 5 — 7 元环；

R^2是含有 5-20 个碳原子并且任选含有 1-4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基，其中所述烃基可以任选被取代；

R^3是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）或 -C_{1-4}烷基 -（任选被取代的芳基）；

R^4是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）或 -C_{1-4}烷基 -（任选被取代的芳基）；

R^5是 -H、-C(O)-（任选被取代的C_{1-6}烷基）或 -（任选被取代的C_{1-6}烷基）；

R^6是 -H、-C(O)-（任选被取代的C_{1-6}烷基）或 -（任选被取代的C_{1-6}烷基）；

R* 是 -H 或 -(C_{1-6}烷基）；且

R** 是 -H、-(C_{1-6}烷基）、-(C_{3-7}环烷基）、-（芳基）或 -C_{1-4}烷基 -（芳基）；

其中所述的烷基的任选的取代基选自卤素、-CN、-NR*R*、-OH 和 -O-C_{1-6}烷基；且

其中所述的环烷基、芳基或烃基的任选的取代基选自 -C_{1-6}烷基、- 卤素、-CF_3、-CN、-X^1-R*、- 芳基和 -C_{1-4}烷基 - 芳基，

其中所述化合物用于治疗、改善或预防病毒疾病。

4. 根据权利要求 3 所述的化合物，其中所述的病毒疾病是由疱疹病毒科、逆转录病毒科、丝状病毒科、副粘病毒科、弹状病毒科、正粘病毒科、本雅病毒科、沙粒病毒科、冠状病毒科、微小核糖核酸病毒科、披膜病毒科、黄热病病毒科引起的。

5. 根据权利要求 4 所述的化合物，其中所述的病毒疾病是流感。

6. 治疗、改善或预防病毒疾病的方法，所述方法包括给需要其的患者施用有效量的权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物，其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。

7. 根据权利要求 6 所述的方法，其中所述的病毒疾病是由疱疹病毒科、逆转录病毒科、丝状病毒科、副粘病毒科、弹状病毒科、正粘病毒科、本雅病毒科、沙粒病毒科、冠状病毒科、微小核糖核酸病毒科、披膜病毒科、黄热病病毒科引起的。

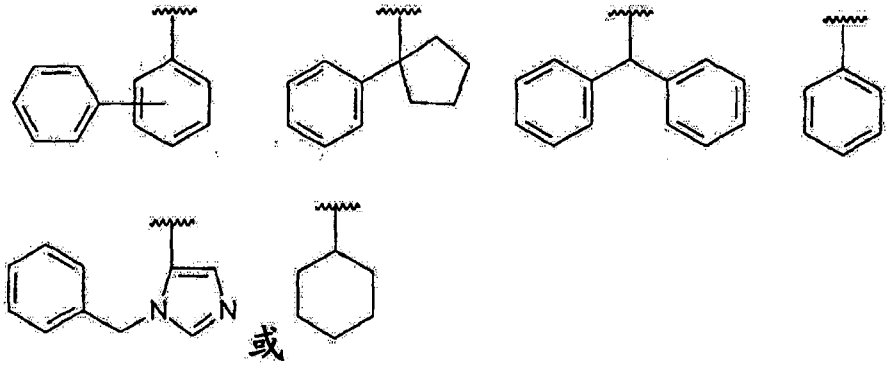
8. 根据权利要求 7 所述的方法，其中所述的病毒疾病是流感。

9. 根据权利要求 1、3、4 或 5 所述的化合物、根据权利要求 2 所述的药物组合物或根据权利要求 6、7 或 8 所述的方法，其中 m 是 1 或 2。

10. 根据权利要求 1、3、4 或 5 所述的化合物、根据权利要求 2 所述的药物组合物或根据权利要求 6、7 或 8 所述的方法，其中 R^1是 -H 或 -（任选被取代的 C_{1-6}烷基）。

11. 根据权利要求 1、3、4 或 5 所述的化合物、根据权利要求 2 所述的药物组合物或根据权利要求 6、7 或 8 所述的方法，其中 R^2是任选被取代的芳基、任选被取代的杂芳基或任选被取代的 C_{5-7}环烷基。

12. 根据权利要求 1、3、4 或 5 所述的化合物、根据权利要求 2 所述的药物组合物或根据权利要求 6、7 或 8 所述的方法，其中 R^2是



或

并且其中的杂环基、苯基、环己基或环戊基可以任选在任意可利用的位置上被取代基取代，所述取代基独立地选自 -C_{1-6}烷基、卤素、-CF_3、-CN、-OH 和 -O-C_{1-6}烷基。

13. 根据权利要求 1、3、4 或 5 所述的化合物、根据权利要求 2 所述的药物组合物或根据权利要求 6、7 或 8 所述的方法，其中 L 是 -$(CH_2)_m$- 或 -NR*-SO_2-。

14. 根据权利要求 1、3、4 或 5 所述的化合物、根据权利要求 2 所述的药物组合物或根据权利要求 6、7 或 8 所述的方法，其中 X^1是 O 或 NR*。

15. 根据权利要求 3 所述的化合物或根据权利要求 6 所述的方法，其中与权利要求 3 所述的化合物同时或相继施用另外的抗病毒药。

16. 药物组合物，其包含：

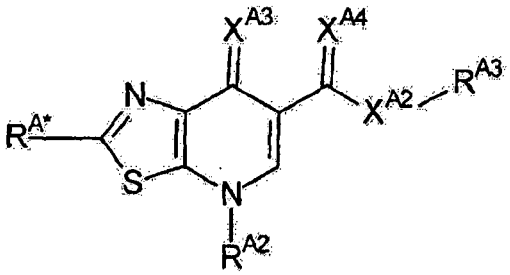
(i) 权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物；和

(ii) 与通式 (Di)、(Dii) 或 (Diii) 的化合物不同的至少一种聚合酶抑制剂；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

17. 根据权利要求 16 所述的药物组合物，其中所述的与通式 (Di)、(Dii) 或 (Diii) 的化合物不同的至少一种聚合酶抑制剂选自

(a) 通式 (A) 的化合物，其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式，



(A)

其中

R^{A*}是 -H、-Hal、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的 C_{3-7}环烷基）、-C_{1-4}烷基 -（任选被取代的芳基）或 $-X^1-R^1$；

X^{A1}是 O、C(O)、C(O)O、OC(O)；S、SO、SO_2、NR^{A4}、$N(R^{A5})C(O)$、$C(O)NR^{A5}$；

X^{A2}是 O、S、NR^{A4}；

X^{A3}是 O 或 S；

X^{A4}是 O 或 S；

R^{A1}是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的 C_{3-7}环烷基）、-C_{1-4}烷基 -（任选被取代的芳基）；

R^{A2}是含有 5-20 个碳原子并且任选含有 1-4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基，其中所述烃基可以是任选被取代的；

R^{A3}是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 -C_{1-4}烷基 -（任选被取代的芳基），如果 X^{A2}是 NR^{A4}，则 R^{A3}也可以是 -OH；

R^{A4}是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的 C_{3-7}环烷基）或 -C_{1-4}烷基 -（任选被取代的芳基），或者如果 X^{A1}是 NR^{A4}，则 R^{A4}和 R^{A1}可以结合在一起形成 5-7 元环，其可以任选含有 O、S 或还有 N，或者如果 X^{A2}是 NR^{A4}，则 R^{A4}和 R^{A3}可以结合在一起形成 5-7 元环，其可以任选含有 O、S 或还有 N；且

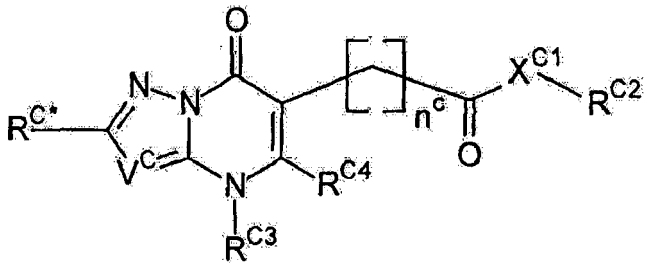
R^{A5}是 -H、-(任选被取代的C_{1-6}烷基)、-(任选被取代的C_{3-7}环烷基)、-(任选被取代的芳基)、-C_{1-4}烷基 -(任选被取代的C_{3-7}环烷基)或 -C_{1-4}烷基 -(任选被取代的芳基);且

R^{A6}是 -H或 -C_{1-6}烷基;

其中所述的烷基的任选的取代基选自卤素、-CN、-$NR^{A6}R^{A6}$、-OH和 -O-C_{1-6}烷基;

其中所述的环烷基、芳基或烃基的任选的取代基选自 -C_{1-6}烷基、卤素、-CF_3、-CN、-$X^{A1}-R^{A5}$和 -C_{1-4}烷基 - 芳基;和

(b) 通式 (C) 的化合物,其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式,



(C)

其中

V^C是N或CR^{C6};

X^{C1}是O、S或NR^{C8};

X^{C2}是NR^{C5}、$N(R^{C5})C(O)$、$C(O)NR^{C5}$、O、C(O)、C(O)O、OC(O);S、SO、SO_2、$SO_2N(R^{C5})$或$N(R^{C5})SO_2$;

R^{C*}是 -H、-Hal、-(任选被取代的C_{1-6}烷基)、-(任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团)、-C_{1-4}烷基 -(任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团)或 -$X^{C2}-R^{C1}$;

R^{C1}是 -H、-(任选被取代的C_{1-6}烷基)、-(任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团)、-C_{1-4}烷基 -(任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团);

R^{C2}是 -H、-(任选被取代的C_{1-6}烷基)、-(任选被取代的C_{3-7}环烷基)、-(任选被取代的芳基)、-C_{1-4}烷基 -(任选被取代的C_{3-7}环烷基)或 -C_{1-4}烷基 -(任选被取代的芳基),或者如果X^{C1}是$NR^{C'}$,则R^{C2}也可以是 -OH;

R^{C3}是 -H、-R^{C7}或 -$X^{C2}-R^{C7}$;

R^{C4}是 -H、-(任选被取代的C_{1-6}烷基)、-(任选被取代的C_{3-7}环烷基)、-(任选被取代的芳基)、-C_{1-4}烷基 -(任选被取代的C_{3-7}环烷基)或 -C_{1-4}烷基 -(任选被取代的芳基);

R^{C5}是 -H、-(任选被取代的C_{1-6}烷基)、-(任选被取代的C_{3-7}环烷基)、-(任选被取代的芳基)、-C_{1-4}烷基 -(任选被取代的C_{3-7}环烷基)或 -C_{1-4}烷基 -(任选被取代的芳基);

R^{C6}是H、-C_{1-6}烷基、- 芳基、卤素或CN;

R^{C7}是 -（任选被取代的含有 5 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基）；

R^{C8}是 -H 或 $-C_{1-6}$烷基；且

n^C是 0 — 4；

其中所述的烷基的任选的取代基选自卤素、-CN、$-NR^{C5}R^{C5}$、-OH 和 $-O-C_{1-6}$烷基；

其中所述的环烷基、芳基、单环或多环基团或烃基的任选的取代基选自 $-C_{1-6}$烷基、卤素、$-CF_3$、-CN、$-X^{C2}-R^{C8}$和 $-C_{1-4}$烷基 - 芳基；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

18. 药物组合物，其包含：

(i) 权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物；和

(ii) 至少一种神经氨酸酶抑制剂；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

19. 药物组合物，其包含：

(i) 权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物；和

(ii) 至少一种 M2 通道抑制剂；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

20. 药物组合物，其包含：

(i) 权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物；和

(ii) 至少一种 α 葡糖苷酶抑制剂；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

21. 药物组合物，其包含：

(i) 权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物；和

(ii) 至少一种另外的流感靶标的配体；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

22. 药物组合物，其包含：

(i) 权利要求 3 中所定义的通式 (Di)、(Dii) 或 (Diii) 的化合物；和

(ii) 至少一种选自抗生素、抗炎药、脂氧化酶抑制剂、EP 配体、缓激肽配体和大麻素配体的药剂；

并且任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

23. 权利要求 16 至 22 中任意一项中所定义的药物组合物，其用于治疗、改善或预防病毒疾病。

24. 治疗、改善或预防病毒疾病的方法，所述方法包括给需要其的患者施用有效量的权利要求 16 至 22 中任意一项中所定义的药物组合物。

25. 根据权利要求 23 所述的药物组合物或根据权利要求 24 所述的方法，其中所述的病毒疾病是由疱疹病毒科、逆转录病毒科、丝状病毒科、副粘病毒科、弹状病毒科、正粘病毒科、本雅病毒科、沙粒病毒科、冠状病毒科、微小核糖核酸病毒科、披膜病毒科、黄热病病毒科引起的；更优选地其中所述的病毒疾病是流感。

26. 根据前面任意一项权利要求所述的化合物、药物组合物或方法，其中通式 (Di)、(Dii) 或 (Diii) 的化合物在本文所公开的 CPE 测定法中在 50 μM 下表现出至少约 30％的％

降低。

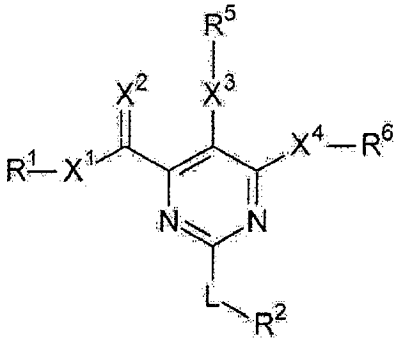
27. 根据前面任意一项权利要求所述的化合物、药物组合物或方法，其中通式 (Di)、(Dii) 或 (Diii) 的化合物在本文所公开的 FRET 内切核酸酶活性测定法中表现出至少约 40 μM 的 IC_{50}。

二羟基嘧啶碳酸衍生物以及它们在治疗、改善或预防病毒疾病中的用途

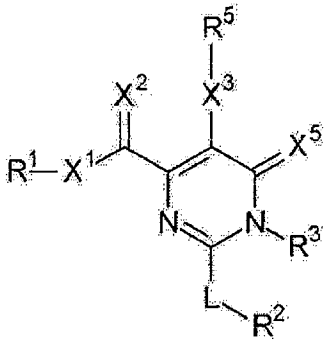
发明领域

[0001] 本发明涉及可用于治疗、改善或预防病毒疾病的通式 (Di)、(Dii) 或 (Diii) 的化合物，其任选是药学上可接受的盐、溶剂合物、多晶型物、共用药物 (codrug)、共晶 (cocrystal)、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。

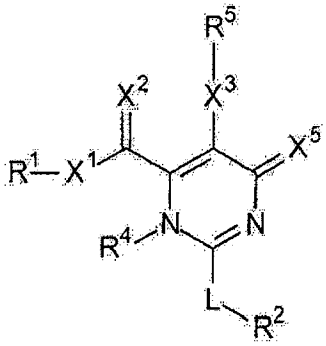
[0002]



(Di)



(Dii)



(Diii)

[0003] 发明背景

[0004] 最近一些年，流感病毒对全球的公共健康所造成的严重威胁已经凸显在以下方面：首先，高致病性鸟 H5N1 病毒株向人类的持续性低水平传播（在被感染的人中死亡率为 63%，http://www.who.int/csr/disease/avian_influenza/en/），第二，在 2009 年出乎预料地出现了新的大流行病毒株 A/H1N1，其已经迅速扩散到全世界 (http://www.who.int/csr/disease/swineflu/en/)。该新病毒株具有高度接触传染性，但目前通常仅产生轻度疾患，同时这种病毒将来的演变是不可预期的。在一种严重得多的、但是高度合理的情形中，H5N1 可能已经在人之间更容易地传播或者新的 A/H1N1 可能已经毒力更强且可能已经携带产生达菲抗药性的单点突变 (Neumann 等，Nature, 2009(18；459(7249)931-939))；如许多季节性 H1N1 病毒株最近已经显示的那样 (Dharan 等，The Journal of the American Medical Association, 2009 年 3 月 11 日；301(10), 1034-1041；Moscona 等，The New England Journal ofMedicine, 2009(3 月 5 日；360(10)pp 953-956))。在这种情况下，生产和使用疫苗的延迟（在 A/H1N1 的较有利的情况下为～ 6 个月，对于 H5N1 而言仍然是没有解决的问题）在人类生活和社会瓦解方面可能已经是灾难性的代价。

[0005] 广泛公认的是，为了跨越获得新疫苗并治疗严重情况以及克服病毒抗药性问题之前的这段时间，需要更宽泛的抗流感药选择。因此，开发新的抗流感药已经再次变得极为迫切（在出现抗神经氨酸酶药后大制药公司已经大半放弃了开发新的抗流感药）。

[0006] 开发抗病毒药的一个良好起点是重要病毒蛋白质的结构信息。因此，例如流感病毒表面抗原神经氨酸酶的晶体结构测定 (Von Itzstein, M. 等，(1993), Nature, 363, pp. 418-423) 直接导致了开发具有抗病毒活性的神经氨酸酶抑

制剂，其阻止病毒从细胞中被释放，但是不阻止病毒产生。随后这些神经氨酸酶抑制剂以及它们的衍生物已经被开发成抗流感药扎那米韦 (Glaxo) 和奥塞米韦 (Roche)，它们目前被许多国家作为对抗可能的大流行病的一线防御措施进行储备。然而，这些药物仅缩短临床疾病的持续时间。或者，其它抗流感化合物例如金刚烷胺和金刚乙胺靶向于干扰细胞内病毒脱壳的病毒膜中的离子通道蛋白，即 M2 蛋白。然而，由于其副作用和迅速发生抗药性病毒突变体，它们已经不被广泛使用 (Magden, J. 等，(2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621)。另外，已经证明另一些非特异性病毒药物例如利巴韦林对治疗流感和其它病毒感染有效 (Eriksson, B. 等，(1977), Antimicrob. Agents Chemother., 11, pp. 946-951)。然而，可能是由于其严重的副作用，利巴韦林仅在少数几个国家获得批准 (Furuta 等, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2005, p. 981 - 986)。显然，需要新的抗病毒化合物，优选对抗不同靶标的新的抗病毒化合物。

[0007] 流感病毒以及索戈托病毒 (Thogotovirus) 属于正粘病毒科家族，正粘病毒科家族以及本雅病毒科 (Bunyaviridae) 家族（包括汉滩病毒属、内罗毕羊病病毒属、正本雅病毒属 (Orthobunyavirus) 和白蛉热病毒属）是负链 RNA 病毒。它们的基因组被分段并以核糖核蛋白颗粒的形式出现，所述核糖核蛋白颗粒包括 RNA 依赖性 RNA 聚合酶，其进行 (i) 单链病毒体 RNA (vRNA) 向病毒 mRNA 中的初始拷贝和 (ii) vRNA 复制。该酶是由亚单位 PA、PB1 和 PB2 构成的三聚体复合物，对病毒的生命周期而言至关重要，因为它负责病毒 RNA 的复制和转录。在以前的工作中，已经鉴定并测定了所述聚合酶的两个关键结构域的原子结构—PB2 亚单位中的 mRNA 帽结合结构域 (Guilligay 等，Nature Structural&Molecular Biology 2008；5 月；15(5)：500-506) 和 PA 亚单位中的内切核酸酶活性部位 (Dias 等，Nature 2009, 458, 914-918)。这两个部位对于流感病毒用于产生病毒 mRNA 的独特的抢帽 (cap-snatching) 转录模式而言很重要。为了生成病毒 mRNA，所述聚合酶利用所谓的“抢帽”机制 (Plotch, S. J. 等，(1981), Cell, 23, pp. 847-858；Kukkonen, S. K. 等 (2005), Arch. Virol., 150, pp. 533-556；Leahy, M. B. 等，(2005), J. Virol., 71, pp. 8347-8351；Noah, D. L. 等，(2005), Adv. Virus Res., 65, pp. 121-145)。5’ 帽（也称为 RNA 帽，RNA 7- 甲基鸟苷帽或 RNA m7G 帽）是已经被加入信使 RNA 的 5’ 末端的修饰的鸟嘌呤核苷酸。所述 5’ 帽由通过 5’-5’- 三磷酸键与第一个转录的核苷酸连接的末端 7- 甲基鸟苷残基组成。所述病毒聚合酶与细胞 mRNA 分子的 5’ RNA 帽结合并将 RNA 帽连同 10-15 个核苷酸的一段序列一起断裂。然后加帽的 RNA 片段用作合成病毒 mRNA 的引物。

[0008] 所述聚合酶复合物似乎是适宜的抗病毒药靶标，因为它对于病毒 mRNA 的合成和病毒复制而言非常重要，并且含有可能与宿主细胞蛋白中发现的功能活性部位显著不同的多种功能活性部位 (Magden, J. 等，(2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621)。因此，例如，已经尝试了用类似于 PB1 内的 PA- 结合结构域的 25- 氨基酸肽来干扰聚合物亚单位的装配 (Ghanem, A. 等，(2007), J. Virol., 81, pp. 7801-7804)。此外，还已经靶向于所述聚合酶的内切核酸酶活性，并且作为流感病毒中这一活性的选择性抑制剂已经鉴定了一系列 4- 取代的 2,4- 二氧代丁酸化合物 (Tomassini, J. 等，(1994), Antimicrob. Agents Chemother., 38, pp. 2827-2837)。另外，已经证明在 Delitschia confertaspora（一个真菌种类）的提取物中鉴定的 flutimide（一种取代的 2,6- 二酮基哌嗪）抑制流感病毒的内切核酸酶 (Tomassini, J. 等，(1996), Antimicrob. Agents Chemother., 40, pp. 1189-1193)。

而且，已经尝试了用核苷类似物例如 2' - 脱氧 -2' - 氟鸟苷干扰病毒转录 (Tisdale, M. 等，(1995), Antimicrob. Agents Chemother., 39, pp. 2454-2458)。

[0009] 在 WO 2004/019933 中公开了一些声称可用于预防或治疗动脉粥样硬化或再狭窄的杂环甲酰胺类化合物。所述化合物被声称由于它们对疱疹病毒的活性而可用于这些应用，因为动脉粥样硬化与许多疱疹病毒感染有关。

[0010] WO 2011/046920 涉及声称适合用于抗微生物疗法的 DXR 抑制剂。

[0011] B. M. Baughman 等使用荧光偏振测定法鉴定了流感内切核酸酶抑制剂 (ACS Chem. Biol. 2012, 7, 526 - 534)。

[0012] 本发明的一个目的是鉴定另外的有效对抗病毒疾病的、具有改善的药理学性质的化合物。

[0013] 发明概述

[0014] 因此，在第一个实施方案中，本发明提供了通式 (Di)、(Dii) 或 (Diii) 的化合物。

[0015] 应当理解的是，在本申请文件中，除非另有说明，否则术语“通式 (Di)、(Dii) 或 (Diii) 的化合物”涵盖药学上可接受的盐、溶剂合物、多晶型物、前药、共用药物、共晶、互变异构体、外消旋物、对映体或非对映体或者其混合物。

[0016] 本发明的另一个实施方案涉及药物组合物，其包含通式 (Di)、(Dii) 或 (Diii) 的化合物和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

[0017] 通式 (Di)、(Dii) 或 (Diii) 的化合物可用于治疗、改善或预防病毒疾病。

[0018] 发明详述

[0019] 在下面详细描述本发明之前，应当理解的是，本发明不限于本文所述的具体的方法、方案和试剂，因为它们可以变化。还应当理解的是，本文所用的术语是仅为了描述具体实施方案，不旨在限制本发明的范围，其将仅由所附的权利要求书来限定。除非另有定义，否则本文所用的所有技术和科学术语具有与本领域技术人员通常理解的含义相同的含义。

[0020] 优选地，本文所用的术语如“A multilingual glossary of biotechnological terms: (IUPAC Recommendations)”, Leuenberger, H. G. W, Nagel, B. 和 **Kölbl**, H. 编辑 (1995), Helvetica Chimica Acta, CH-4010 巴塞尔，瑞士中所述的那样进行定义。

[0021] 除非上下文另有要求，否则在本说明书和随后的权利要求书中，词语“包含”及其变体例如“包括”和“含有”均应理解为表示包括所给出的整数或步骤或者整数组或步骤组，但是不排除任何其它整数或步骤或者整数组或步骤组。在下面的段落中，更详细地定义了本发明的不同方面。如此定义的每个方面可以与任意另外的一个或多个方面组合，有清楚的相反显示时除外。特别地，所给出的任意优选的或有利的特征可以与任意另外的一个或多个优选的或有利的特征组合。

[0022] 在本说明书的文本中引用了多个文献。无论是上文引用的，还是下文引用的，将本文所引用的每篇文献 (包括所有专利、专利申请、科学出版物、制造商说明书、使用说明等) 通过引用整体合并入本文中。本文中的任何内容均不应理解为承认这类公开内容构成本发明的现有技术。

[0023] 定义

[0024] 术语“烷基”指饱和的直链或支链碳链。

[0025] 术语“环烷基”表示环形式的“烷基”。术语“环烷基”还包括其二环、三环和多环

形式。除非另有规定，否则环烷基可具有 3 - 12 个碳原子。

[0026] 术语“环状杂烷基”包括单环、二环、三环和多环的杂烷基。除非另有规定，否则环状杂烷基可具有 3 - 12 个碳原子并且可以包括一个或多个选自 N、O 或 S 的杂原子。

[0027] “Hal”或“卤素”表示 F、Cl、Br 和 I。

[0028] 术语“芳基”优选指含有 6 个碳原子的芳族单环、含有 10 个碳原子的芳族二环环系或含有 14 个碳原子的芳族三环环系。实例有苯基、萘基或蒽基，优选苯基。

[0029] 术语“杂芳基”优选指 5 或 6 元芳族环，其中环中的一个或多个碳原子已经被 1、2、3 或 4 个（对于 5 元环而言）或者 1、2、3、4 或 5 个（对于 6 元环而言）相同或不同的杂原子代替，其中所述杂原子选自 O、N 和 S。杂芳基的实例包括吡咯、吡咯烷、氧杂环戊烷、呋喃、咪唑烷、咪唑、吡唑、噁唑烷、噁唑、噻唑、哌啶、吡啶、吗啉、哌嗪和二氧戊环。

[0030] 术语“含有 5 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基”指具有 5 - 20 个碳原子并且任选具有 1 - 4 个选自 O、N 和 S 的任意基团，只要该基团含有至少一个环即可。该术语还包括其二环、三环和多环形式。如果存在多于一个的环，则它们可以是彼此分开的或稠合的。所述的一个或多个环可以是碳环或杂环，并且可以是饱和的、不饱和的或芳族的。碳原子和杂原子可以均存在于所述的一个或多个环中，或者碳原子和 / 或杂原子中的一些可以存在于环外，例如，存在于连接基团（例如 $-(CH_2)_p-$，其中 p = 1 - 6）中。这些基团的实例包括 -（任选被取代的 C_{3-7} 环烷基）、-（任选被取代的芳基），其中所述的芳基可以是例如苯基、-（任选被取代的联苯基）、金刚烷基、-（C_{3-7} 环烷基）- 芳基，以及具有连接基团的相应化合物。这些基团的另外的实例包括含有例如 1-3 个 N 原子的 -（任选被取代的 3-7 元环状杂烷基）或 -（任选被取代的杂芳基）。

[0031] 术语“（任选被取代的含有 3 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的单环或多环基团）”指含有 3 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的任意单环或多环基团。该术语包括其单环、二环、三环和多环形式。如果存在多于一个的环，则它们可以是彼此分开的或稠合的。所述的一个或多个环可以是碳环或杂环，并且可以是饱和的、不饱和的或芳族的。碳原子和杂原子可以均存在于所述的一个或多个环中，或者碳原子和 / 或杂原子中的一些可以存在于环外，例如，存在于连接基团（例如 $-(CH_2)_p-$，其中 p = 1 - 6）中。这些基团的实例包括 -（任选被取代的 C_{3-7} 环烷基）和 -（任选被取代的芳基），其中所述的芳基可以是例如苯基或蒽基，以及具有连接基团的相应化合物。

[0032] 如果一个化合物或基团被称为是“任选被取代的”，则它在每种情况下可以包括一个或多个所给出的取代基，其中所述取代基可以相同或不同。

[0033] 术语“药学上可接受的盐”指本发明的化合物的盐。适合的药学上可接受的盐包括酸加成盐，其可以例如通过将本发明的化合物的溶液与药学上可接受的酸的溶液混合来形成，所述的药学上可接受的酸例如盐酸、硫酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、柠檬酸、酒石酸、碳酸或磷酸。此外，在化合物带有酸性基团的情况下，其适合的药学上可接受的盐可以包括碱金属盐（例如，钠盐或钾盐）；碱土金属盐（例如，钙盐或镁盐）；以及与适合的有机配体形成的盐（例如，铵盐、季铵盐和使用抗衡阴离子如卤素离子、氢氧根、羧酸根、硫酸根、磷酸根、磷酸根、硝酸根、烷基磺酸根和芳基磺酸根形成的胺阳离子）。药学上可

接受的盐的举例说明性实例包括但不限于乙酸盐、己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、硫酸氢盐、酒石酸氢盐、硼酸盐、溴化物、丁酸盐、乙二胺四乙酸钙盐 (calcium edetate)、樟脑酸盐、樟脑磺酸盐、樟磺酸盐、碳酸盐、氯化物、柠檬酸盐、克拉维酸盐 (clavulanate)、环戊烷丙酸盐、二葡糖酸盐、二盐酸盐、十二烷基硫酸盐、乙二胺四乙酸盐、乙二磺酸盐、依托酸盐、乙磺酸盐、乙烷磺酸盐、甲酸盐、富马酸盐、葡庚糖酸盐、葡萄糖庚酸盐 (glucoheptonate)、葡糖酸盐、谷氨酸盐、甘油磷酸盐、乙醇酰阿散酸盐 (glycolylarsanilate)、半硫酸盐、庚酸盐、己酸盐、己基间苯二酚盐、哈胺 (hydrabamine)、氢溴酸盐、盐酸盐、氢碘酸盐、2- 羟基 - 乙烷磺酸盐、羟基萘酸盐、碘化物、异硫代硫酸盐 (isothionate)、乳酸盐、乳糖酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、马来酸盐、丙二酸盐、扁桃酸盐、甲磺酸盐、甲烷磺酸盐、甲基硫酸盐、粘酸盐、2- 萘磺酸盐、萘磺酸盐、烟酸盐、硝酸盐、N- 甲基葡糖胺铵盐、油酸盐、草酸盐、扑酸盐（双羟萘酸盐）、棕榈酸盐、泛酸盐、果胶酯酸盐、过硫酸盐、3- 苯基丙酸盐、磷酸盐 / 二磷酸盐、苦味酸盐、新戊酸盐、聚半乳糖醛酸盐、丙酸盐、水杨酸盐、硬脂酸盐、硫酸盐、碱式乙酸盐 (subacetate)、琥珀酸盐、单宁酸盐、酒石酸盐、茶氯酸盐、甲苯磺酸盐、triethiodide、十一烷酸盐、戊酸盐等（参见例如 S. M. Berge 等，"Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977))。

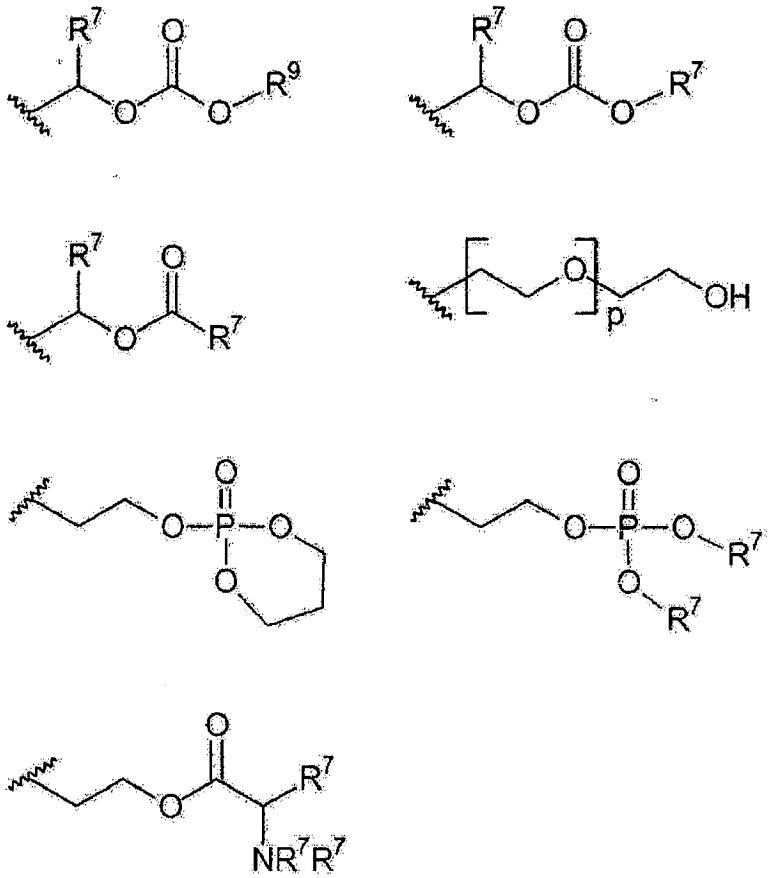
[0034] 当本发明的化合物是结晶形式时，该结构可以含有溶剂分子。所述溶剂典型地是药学上可接受的溶剂，尤其包括水（水合物）或有机溶剂。可能的溶剂合物的实例包括乙醇合物和异丙醇合物。

[0035] 术语“共用药物”指通过共价化学键键合的两种或更多种治疗化合物。详细的定义可见于例如 N. Das 等，European Journal of Pharmaceutical Sciences, 41, 2010, 571 - 588。

[0036] 术语“共晶”指一种多组分晶体，其中所有组分当是其纯形式时在环境条件下均是固体。这些组分以化学计量比或非化学计量比的靶标分子或离子（即，本发明的化合物）和一种或多种中性分子共晶形成物的形式共存。详细讨论可见于例如 Ning Shan 等，Drug Discovery Today, 13 (9/10), 2008, 440-446 和 D. J. Good 等，Cryst. Growth Des., 9 (5), 2009, 2252 - 2264 中。

[0037] 本发明的化合物也可以是前药（即其在体内代谢成活性代谢物的化合物）的形式。适合的前药是例如酯。适合基团的具体实例尤其在 US2007/0072831 的第 [0082] - [0118] 段在标题前药和保护基下给出。如果 X^1 是 O 或 S，则优选的前药实例包括其中 R^1 被下列基团之一代替的化合物：

[0038]



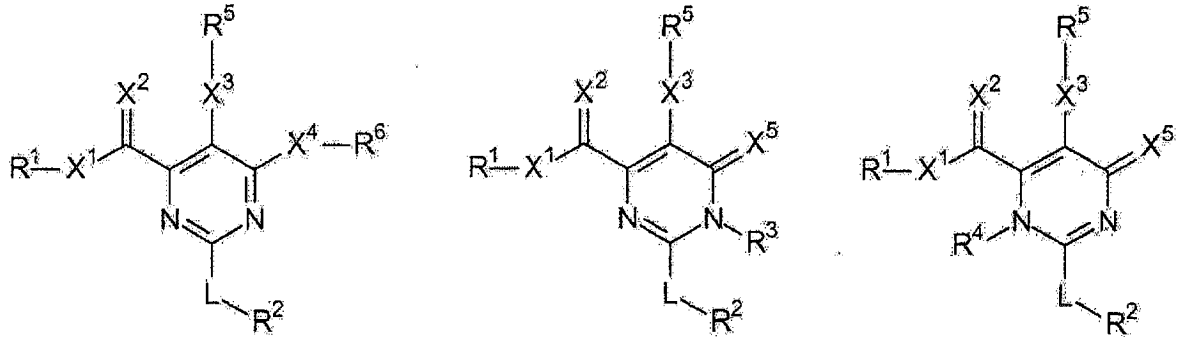
[0039] 在这些结构式中，R^7可以相同或不同。R^9是环状基团，例如芳基或C_{3-7}环烷基。p是2-8。

[0040] 如果X^1是NR*，则优选的前药实例包括其中R^1和R*不都是H的化合物。

[0041] 通式(Di)、(Dii)或(Diii)的化合物

[0042] 本发明提供了通式(Di)、(Dii)或(Diii)的化合物。

[0043]



(Di) (Dii) (Diii)

[0044] 本发明提供了通式(Di)、(Dii)或(Diii)的化合物，其中适用下列定义。

[0045] X^1是O、S或NR*；优选O或NR*。

[0046] X^2是O或S；优选O。

[0047] X^3是O或S；优选O。

[0048] X^4是 O 或 S；优选 O。

[0049] X^5是 O 或 S；优选 O。

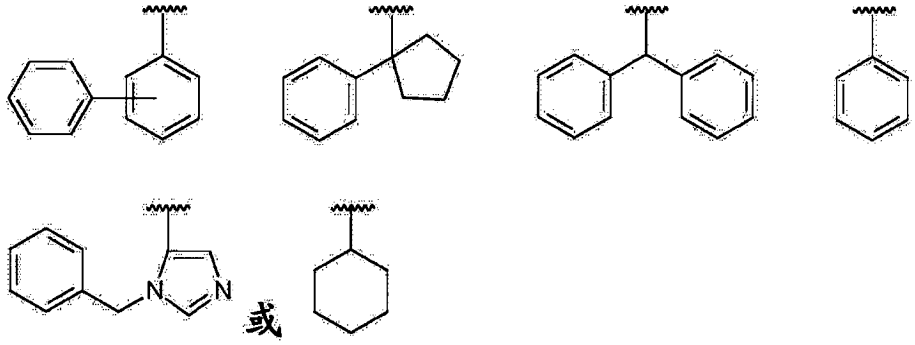
[0050] L 是 $-(CH_2)_m-$、$-NR^*-SO_2-$ 或 $-SO_2-NR^*-$；优选 $-(CH_2)_m-$ 或 $-NR^*-SO_2-$。

[0051] m 是 1-4；优选 m 是 1 或 2；更优选 m 是 1。

[0052] R^1是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的芳基）、-C(O)-O-R** 或 $-P(O)(OR^{**})_2$。如果 X^1是 NR*，则 R^1和 R* 可以任选地结合在一起形成 5 — 7 元环。优选 R^1是 -H 或 -（任选被取代的 C_{1-6}烷基）。

[0053] R^2是含有 5-20 个碳原子并且任选含有 1-4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基，其中所述烃基可以任选被取代。优选 R^2是任选被取代的芳基、任选被取代的杂芳基或任选被取代的 C_{5-7}环烷基，更优选 R^2选自

[0054]



[0055] 其中杂环基、苯基、环己基或环戊基可以任选在任意可利用的位置上被取代基取代，所述取代基独立地选自 $-C_{1-6}$烷基、卤素、$-CF_3$、-CN、-OH 和 $-O-C_{1-6}$烷基。

[0056] R^3是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 $-C_{1-4}$烷基 -（任选被取代的芳基）。

[0057] R^4是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）或 $-C_{1-4}$烷基 -（任选被取代的芳基）。

[0058] R^5是 -H、-C(O)-（任选被取代的 C_{1-6}烷基）或 -（任选被取代的 C_{1-6}烷基）。

[0059] R^6是 -H、-C(O)-（任选被取代的 C_{1-6}烷基）或 -（任选被取代的 C_{1-6}烷基）。

[0060] R* 是 -H 或 $-(C_{1-6}$烷基）；优选 -H。

[0061] R** 是 -H、$-(C_{1-6}$烷基）、$-(C_{3-7}$环烷基）、-（芳基）或 $-C_{1-4}$烷基 -（芳基）；优选 $-(C_{1-6}$烷基）或 -（芳基）。

[0062] 烷基的任选的取代基选自卤素、-CN、-NR*R*、-OH 和 $-O-C_{1-6}$烷基。

[0063] 环烷基、芳基或烃基的任选的取代基选自 $-C_{1-6}$烷基、- 卤素、$-CF_3$、-CN、$-X^1-R^*$、- 芳基和 $-C_{1-4}$烷基 - 芳基。

[0064] 本发明的发明人已经令人惊讶地发现，具有 $-L-R^2$所示的庞大疏水性基团的本发明的化合物与在该位置上具有较少空间需求的基团的相应化合物相比具有改善的药理学性质。不希望受理论的束缚，认为病毒聚合酶蛋白质具有用于结合的口袋并且本发明的化合物的这种疏水性基团与其它基团相比具有改善的结合。这是根据现有技术不能预测的或预期的。

[0065] 本发明的化合物可以以药物组合物的形式施用于患者，所述药物组合物可任选包

含一种或多种药学上可接受的赋形剂和 / 或载体。

[0066] 本发明的化合物可以通过各种公知的途径施用，包括口服、直肠、胃内(intragastrical)、颅内和肠胃外施用，例如静脉内、肌内、鼻内、真皮内、皮下，以及类似的施用途径。特别优选的是口服、鼻内和肠胃外施用。根据施用途径，需要不同的药物制剂，这些施用途径中的一些可能需要给药物制剂涂敷保护性包衣以防止本发明的化合物在例如消化道内降解。

[0067] 因此，优选地，本发明的化合物被配制成糖浆、输液或注射液、喷雾剂、片剂、胶囊、囊片 (capslet)、锭剂、脂质体、栓剂、膏药、绷带 (band-aid)、延迟释放胶囊 (retard capsule)、散剂或缓慢释放制剂。优选地，稀释剂是水、缓冲剂、缓冲盐溶液或盐溶液，载体优选选自可可脂和 vitebesole。

[0068] 用于施用本发明的化合物的特别优选的药物形式是适合注射使用的形式，包括无菌的水性溶液或分散体和用于即时制备无菌注射溶液或分散体的无菌粉末。在所有情况中，最终的溶液或分散体形式必须是无菌的并且是流体。典型地，这类溶液或分散体将包含溶剂或分散介质，其含有例如水 - 缓冲水溶液例如生物相容性的缓冲剂、乙醇、多元醇例如甘油、丙二醇、聚乙二醇、其适合的混合物，表面活性剂或植物油。本发明的化合物也可以被配制成脂质体，特别是用于肠胃外施用的脂质体。脂质体提供在循环中半衰期增加的优点（如果与游离药物相比）以及所包裹的药物的延长的更均匀的释放。

[0069] 输液和注射液的灭菌可以通过任意数量的本领域公认的技术来实现，包括但不限于加入防腐剂如抗细菌剂或抗真菌剂，例如尼泊金酯 (parabene)、三氯叔丁醇、苯酚、山梨酸或硫柳汞 (thimersal)。此外，还可以在输液和注射液中掺入等张剂，例如糖或盐，特别是氯化钠。

[0070] 含有一种或多种本发明的化合物的无菌注射液的生产通过以下方法完成：将所需量的各化合物掺入酌情具有上面列出的各种成分的适宜溶剂中，然后灭菌。为了获得无菌粉末，将上述溶液按照需要真空干燥或冷冻干燥。本发明的优选的稀释剂是水、生理学上可接受的缓冲剂、生理学上可接受的缓冲盐溶液或盐溶液。优选的载体是可可脂和 vitebesole。可以与本发明的化合物的各种药物形式一起使用的赋形剂可选自下面的非限制性列表：

[0071] a) 粘合剂，例如乳糖、甘露醇、结晶山梨醇、磷酸氢盐、磷酸钙盐 (calcium phosphates)、糖、微晶纤维素、羧甲基纤维素、羟乙基纤维素、聚乙烯吡咯烷酮等；

[0072] b) 润滑剂，例如硬脂酸镁、滑石粉、硬脂酸钙、硬脂酸锌、硬脂酸、氢化植物油、亮氨酸、甘油酯和硬脂酰醇富马酸钠，

[0073] c) 崩解剂，例如淀粉、交联羧甲基纤维素、甲基纤维素钠、琼脂、膨润土、海藻酸、羧甲基纤维素、聚乙烯吡咯烷酮等。

[0074] 在一个实施方案中，制剂用于口服施用，并且制剂包含下列成分中的一种或多种或全部：预胶化淀粉、滑石粉、聚乙烯吡咯烷酮 K 30、交联羧甲基纤维素钠、硬脂酰醇富马酸钠、明胶、二氧化钛、山梨醇、柠檬酸一钠、黄原胶、二氧化钛、矫味剂、苯甲酸钠和糖精钠。

[0075] 如果在一个优选的实施方案中本发明的化合物被鼻内施用，其可以以干粉末吸入器或来自使用适合的抛射剂例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷、氢氟烷如 1,1,1,2- 四氟乙烷 (HFA 134A™) 或 1,1,1,2,3,3,3- 七氟丙烷 (HFA 227EA™)、二氧化碳、或

其它适合的气体的加压容器、泵、喷雾器或雾化器中的喷雾剂的形式被施用。所述的加压容器、泵、喷雾器或雾化器可以含有本发明的化合物的溶液或混悬液，例如使用乙醇和抛射剂作为溶剂的溶液或混悬液，其还可以含有润滑剂，例如三油酸山梨坦。

[0076] 其它适合的赋形剂可见于美国药学协会(American Pharmaceutical Association)出版的药物赋形剂手册(Handbook of Pharmaceutical Excipients)，通过引用将其合并入本文。

[0077] 应当理解的是，根据可用本发明的化合物之一治疗的障碍的严重性和具体类型，以及根据待治疗的各个患者例如患者的总体健康状态等，需要不同剂量的各化合物来产生治疗或预防效果。适宜剂量的确定由主治医师酌情确定。认为在本发明的治疗或预防应用中本发明的化合物的剂量应当在约 0.1mg 至约 1g 活性成分(即，本发明的化合物)/千克体重范围内。然而，在一个优选的本发明的应用中，将本发明的化合物以 1.0-500mg/kg 体重、优选 1-200mg/kg 体重的量施用于需要其的个体。用本发明的化合物治疗的持续时间将根据所治疗的疾病的严重性以及每个单个患者的情况和特质反应而变化。在一个优选的预防或治疗应用的实施方案中，每天给成年人口服施用 10mg - 200mg 化合物，这取决于疾病的严重性和/或暴露于疾病载体的程度。

[0078] 如本领域中已知的那样，给定化合物的药学有效量还取决于施用途径。一般而言，如果施用是通过胃肠道(例如用栓剂)、直肠或通过胃内探针进行，则所需的量较高，如果施用途径是肠胃外例如静脉内，则所需的量较低。典型地，如果使用直肠或胃内施用，则本发明的化合物将以 50mg - 1g/kg 体重、优选 10mg - 500mg/kg 体重被施用，如果使用肠胃外施用，则本发明的化合物将以 1 - 100mg/kg 体重被施用。对于鼻内施用，使用 1 - 100mg/kg 体重。

[0079] 如果已知一个人具有发生可用本发明的化合物治疗的疾病的风险，则可以预防性施用生物学活性血清或本发明的药物组合物。在这些情况下，本发明的各化合物优选以天为基础用上述优选的和特别优选的剂量被施用。优选地，每天一次 0.1mg - 1g/kg 体重，优选 10 - 200mg/kg 体重。该施用可以持续至发生各病毒性障碍的风险已经减小。然而，在大部分情况下，在已经诊断出疾病/障碍后施用本发明的化合物。在这些情况中，优选的是每天施用首剂量的本发明的化合物一次、两次、三次或四次。

[0080] 本发明的化合物特别可用于治疗、改善或预防病毒疾病。对病毒疾病的类型没有特别限制。可能的病毒疾病的实例包括但不限于由以下病毒引起的病毒疾病：痘病毒科、疱疹病毒科、腺病毒科、乳头瘤病毒科(Papillomaviridae)、多瘤病毒科(Polyomaviridae)、微小病毒科、嗜肝脱氧核糖核酸病毒科、逆转录病毒科、呼肠孤病毒科、丝状病毒科、副粘病毒科、弹状病毒科、正粘病毒科、本雅病毒科、沙粒病毒科、冠状病毒科、微小核糖核酸病毒科、肝炎病毒科(Hepeviridae)、嵌杯样病毒科、星状病毒科(Astroviridae)、披膜病毒科、黄热病病毒科、δ 病毒属(Deltavirus)、博尔纳病毒科(Bornaviridae)和朊病毒。优选由疱疹病毒科、逆转录病毒科、丝状病毒科、副粘病毒科、弹状病毒科、正粘病毒科、本雅病毒科、沙粒病毒科、冠状病毒科、微小核糖核酸病毒科、披膜病毒科、黄热病病毒科引起的病毒疾病，更优选由正粘病毒科引起的病毒疾病。

[0081] 在下面的表中给出了各种病毒的实例。

[0082]

家族	病毒(优选的实例)
痘病毒科	天花病毒 接触传染性软疣病毒
疱疹病毒科	单纯疱疹病毒 水痘-带状疱疹病毒 巨细胞病毒 EB病毒 卡波西肉瘤相关疱疹病毒(Kaposi's sarcoma-associated herpesvirus)
腺病毒科	人腺病毒A-F
乳头瘤病毒科	乳头瘤病毒
多瘤病毒科	BK-病毒 JC-病毒
微小病毒科	B19病毒 腺相关病毒2/3/5
嗜肝脱氧核糖核酸病毒科	乙型肝炎病毒
逆转录病毒科	人类免疫缺陷病毒 1/2型 人类T细胞白血病病毒 人泡沫病毒(Human foamy virus)
呼肠孤病毒科	呼肠孤病毒1/2/3 轮状病毒A/B/C 科罗拉多蜱热病毒
丝状病毒科	埃博拉病毒 马尔堡病毒

[0083]

副粘病毒科	副流感病毒 1-4 腮腺炎病毒 麻疹病毒 呼吸道合胞病毒 亨德拉病毒(Hendravirus)
弹状病毒科	水泡性口炎病毒 狂犬病病毒 莫科拉病毒 欧洲蝙蝠病毒(European bat virus) 杜文海格病毒(Duvenhage virus)
正粘病毒科	流感病毒A-C型
本雅病毒科	加里福尼亚脑炎病毒(California encephalitis virus) 拉克罗斯病毒 汉坦病毒 普马拉病毒 辛诺柏病毒(Sin Nombre virus) 汉城病毒(Seoul virus) 克里米亚刚果出血热病毒(Crimean-Congo hemorrhagic fever virus) 萨哈林病毒(Sakhalin virus) 裂谷热病毒 白蛉热病毒 乌库尼米病毒(Uukuniemi virus)

[0084]

沙粒病毒科	拉沙热病毒 淋巴细胞性脉络丛脑膜炎病毒 瓜那瑞托病毒(Guanarito virus) 鸠宁病毒, 马丘博病毒 萨比亚病毒(Sabia virus)
冠状病毒科	人冠状病毒
微小核糖核酸病毒科	人肠道病毒A-D型(脊髓灰质炎病毒、埃可病毒、柯萨奇病毒A/B) 鼻病毒A/B/C型 甲型肝炎病毒 双埃柯病毒(Parechovirus) 口蹄疫病毒(Food and mouth disease virus)
肝炎病毒科	戊型肝炎病毒
嵌杯样病毒科	诺沃克病毒 札幌病毒(Sapporo virus)
星状病毒科	人星状病毒(Human astrovirus) 1
披膜病毒科	罗斯河病毒 切昆贡亚病毒 翁尼翁-尼翁病毒 风疹病毒

[0085]

黄热病病毒科	蜱传脑炎病毒(Tick-borne encephalitis virus) 登革热病毒 黄热病病毒 日本脑炎病毒 墨累谷病毒(Murray Valley virus) 圣路易斯脑炎病毒 西尼罗河病毒 丙型肝炎病毒 庚型肝炎病毒(Hepatitis G virus) 庚型乙型肝炎病毒(Hepatitis GB virus)
δ病毒属	δ肝炎病毒
博尔纳病毒科	博尔纳病毒(Bornavirus)
朊病毒	

[0086] 优选地，本发明的化合物用于治疗流感。在本发明内，术语“流感”包括甲型流感、乙型流感、丙型流感、传染性鲑鱼贫血病（isavirus）流感和托高土病毒（thogotovirus）流感，还包括鸟流感（bird flu）和猪流感。对待治疗的个体没有特别限制，其可以是任意脊椎动物，例如鸟和哺乳动物（包括人）。

[0087] 不希望受理论束缚，认为本发明的化合物能抑制内切核酸酶活性、特别是流感病毒的内切核酸酶活性。更具体地，认为它们直接干扰具有内切核酸酶活性的流感PA蛋白的N-末端部分。然而，将化合物递送入细胞内可能有问题，这取决于例如化合物的溶解性或其通过细胞膜的能力。本发明不仅证明了要求保护的化合物在体外具有聚合酶抑制活性，而且还证明了其在体内具有抗病毒活性。

[0088] 式(Di)、(Dii)、(Diii)、(A)和/或(C)的化合物的体外聚合酶抑制活性的一种可能测定法是本文所公开的FRET内切核酸酶活性测定法。优选地，在该FRET测定法中所述化合物在25μM下表现出至少约50％的％降低。在该语境中，％降低是与未处理的样品相比化合物处理的样品的底物裂解的初始反应速度(v0)的％降低。优选地，在该FRET测定法中所述化合物表现出至少约40μM、更优选至少约20μM的IC_{50}。半数最大抑制浓度(IC_{50})是化合物抑制生物学或生物化学功能的有效性的量度，是由从最大100μM- 至少2nM范围内的给定浓度系列的初始反应速度(v0)计算得到的。

[0089] 式(Di)、(Dii)、(Diii)、(A)和/或(C)的化合物的体内抗病毒活性的一种可能测定法是本文所公开的CPE测定法。优选地，所述化合物在50μM下表现出至少约30％的％降低。在该语境中，用化合物处理后病毒介导的细胞致病作用(CPE)的降低是如下计算的：使用基于ATP的细胞生存力测定法(Promega)测定感染的处理的细胞和未感染的处理的细胞的细胞生存力。从感染的处理的样品的相对荧光单位(RLU)响应减去感染的未处理的样品的相对荧光单位(RLU)响应，然后用相应的未感染的样品的生存力归一化，得到％CPE

降低。优选地，所述化合物在该 CPE 测定法中表现出至少约 45 μM、更优选至少约 10 μM 的 IC_{50}。半数最大抑制浓度 (IC_{50}) 是化合物抑制生物学或生物化学功能的有效性的量度，是由从最大 100 μM - 至少 100nM 范围内的给定浓度系列的 RLU 响应计算得到的。

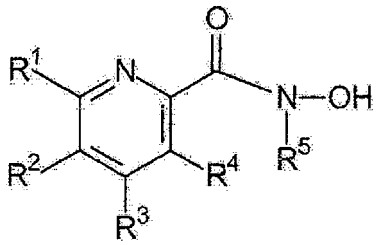
[0090] 通式 (Di)、(Dii)、(Diii) 的化合物可以与一种或多种其它药剂组合使用。对所述的其它药剂的类型没有特别限制，取决于待治疗的障碍。优选地，所述的其它药剂是可用于治疗、改善或预防病毒疾病的另外的药剂，更优选是可用于治疗、改善或预防流感的另外的药剂。

[0091] 下面的药剂组合被认为是特别适合的：

[0092] (i) 内切核酸酶和帽结合抑制剂（特别是靶向于流感的）的组合。对所述的内切核酸酶抑制剂没有特别限制，可以是任意内切核酸酶抑制剂，特别是任意病毒内切核酸酶抑制剂。优选的内切核酸酶抑制剂是 2011 年 10 月 21 日提交的序号为 61/550,045 的美国申请中所定义的具有通式 (I) 结构的那些，通过引用将其全部公开内容合并入本文。特定地，将关于 US 61/550,045 的化合物的通式、各取代基的优选实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。

[0093] 该参考文献的通式 (I) 的化合物可以任选地是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。它们的定义如下（其中在该早期申请中给出的各基团的定义均适用）：

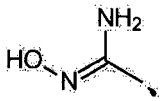
[0094]



(I)

[0095] 其中

[0096] R^1选自 -H、$-C_{1-6}$烷基、-(C_{3-7}环烷基）和 $-CH_2-$(C_{3-7}环烷基）；

[0097] R^2选自 -H、  $-C_{1-6}$烷基、-Hal、-(C_{3-7}环烷基）、$-CH_2-$(C_{3-7}环烷基）、$-(CH_2)_m-$（任选被取代的芳基）、-（任选被取代的含有至少一个选自 N、O 和 S 的杂原子的 5 或 6 元杂环，其中所述取代基选自 $-C_{1-4}$烷基、- 卤素、-CN、$-CHal_3$、- 芳基、$-NR^6R^7$和 $-CONR^6R^7$；

[0098] R^3选自 -H、$-C_{1-6}$烷基、

[0099] $-(CH_2)_n-NR^6R^8$、

[0100] -（任选被取代的 5 或 6 元碳环或杂环，其中所述杂环含有至少一个选自 N、O 和 S 的杂原子），其中所述取代基选自 -Hal、$-C_{1-4}$烷基、$-NR^9R^{10}$、$-(CH_2)_n-OH$、$-C(O)-NR^9R^{10}$、$-SO_2-NR^9R^{10}$、$-NH-C(O)-O-R^{11}$、$-C(O)-O-R^{11}$和含有至少一个选自 N、O 和 S 的杂原子的 5 或 6 元杂环；

[0101] 或者其中 R^1和 R^2一起形成苯基环，或者其中 R^2和 R^3一起形成苯基环；

[0102] R^4是 -H；

[0103] R^5选自 -H 或 $-(CH_2)_n-$（任选被取代的芳基），其中所述取代基选自 -Hal 和 $-C_{1-4}$烷基；或者其中 R^4和 R^5一起形成亚甲基 $-CH_2-$、亚乙基 $-CH_2CH_2-$ 或乙炔基 -CHCH-，其可以任选被 $-C_{1-4}$烷基、- 卤素、$-CHal_3$、$-R^6R^7$、$-OR^6$、$-CONR^6R^7$、$-SO_2R^6R^7$、芳基或杂芳基取代；

[0104] R^6选自 -H 和 $-C_{1-4}$烷基；

[0105] R^7选自 -H 和 $-C_{1-4}$烷基；

[0106] R^8选自 -H、$-C_{1-6}$烷基、$-(CH_2)_n-$（任选被取代的芳基）、$-SO_2-(CH_2)_n-$（任选被取代的芳基）、$-SO_2-(CH_2)_n-$（任选被取代的含有至少一个选自 N、O 和 S 的杂原子的 5-10 元单环或二环杂环）、$-(CH_2)_n-$（任选被取代的含有至少一个选自 N、O 和 S 的杂原子的 5 或 6 元杂环），其中所述取代基选自 -Hal、$-CF_3$、$-C_{1-4}$烷基和 $-(CH_2)_n-$ 芳基；

[0107] R^9选自 -H、$-C_{1-4}$烷基和 $-C_{1-4}$亚烷基 $-NR^{11}R^{11}$；

[0108] R^{10}选自 -H、$-C_{1-4}$烷基和 $-C_{1-4}$亚烷基 $-NR^{11}R^{11}$；

[0109] R^{11}选自 -H、$-CF_3$和 $-C_{1-4}$烷基；

[0110] 每个 m 是 0 或 1；且

[0111] 每个 n 独立地是 0、1、2 或 3。

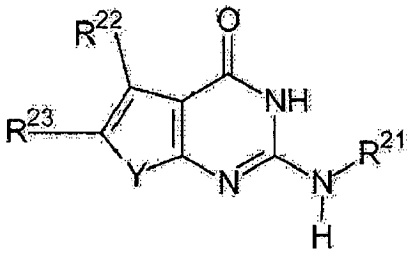
[0112] 另外的优选的内切核酸酶抑制剂是代理律师案卷编号为 T3448US 的共同待审的申请中所定义的通式 (A) 的那些，通过引用将该申请的全部公开内容合并入本文。特定地，将关于通式 (A) 的化合物的通式、各取代基的优选实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。通式 (A) 的化合物可以任选地是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。下文对它们进行了定义。

[0113] 另外的优选的内切核酸酶抑制剂是与代理律师案卷编号为 T3450 US 的共同待审的申请中所定义的通式 (C) 的那些，通过引用将该申请的全部公开内容合并入本文。特定地，将关于通式 (C) 的化合物的通式、各取代基的优选实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。通式 (C) 的化合物可以任选地是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。下文对它们进行了定义。

[0114] 对所述的帽结合抑制剂也没有特别限制，可以是任意帽结合抑制剂，特别是任意病毒帽结合抑制剂。优选的帽结合抑制剂是美国申请 61/550,057 中所定义的具有通式 (II) 结构的那些和 / 或 WO2011/000566 中所公开的化合物，通过引用将其全部公开内容合并入本文。特定地，将关于 US 61/550,057 或 WO2011/000566 的化合物的通式、各取代基的优选实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。

[0115] 通式 (II) 的化合物可以任选地是药学上可接受的盐、溶剂合物、多晶型物、共用药物、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物的形式。其定义如下：

[0116]



(II)

[0117] 其中

[0118] Y 是 S；

[0119] R^{21}选自 -H、$-C_{1-6}$烷基、$-(CH_2)_q-$ 芳基、$-(CH_2)_q-$ 杂环基、$-(CH_2)_q-$ 环烷基、$-(CH_2)_p-OR^{25}$和 $-(CH_2)_p-NR^{25}R^{26}$；

[0120] R^{22}选自 -H、$-C_{1-6}$烷基、$-(CH_2)_q-$ 环烷基、-Hal、$-CF_3$和 -CN；

[0121] R^{23}选自 - 芳基、- 杂环基、- 环烷基、$-C(-R^{28})(-R^{29})-$ 芳基、$-C(-R^{28})(-R^{29})-$ 杂环基和 $-C(-R^{28})(-R^{29})-$ 环烷基；

[0122] R^{25}选自 -H、$-C_{1-6}$烷基和 $-(CH_2CH_2O)_rH$；

[0123] R^{26}选自 -H 和 $-C_{1-6}$烷基；

[0124] R^{27}独立地选自 $-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基、-Hal、$-CF_3$、-CN、$-COOR^{25}$、$-OR^{25}$、$-(CH_2)_qNR^{25}R^{26}$、$-C(O)-NR^{25}R^{26}$和 $-NR^{25}-C(O)-C_{1-6}$烷基；

[0125] R^{28}和 R^{29}独立地选自 -H、$-C_{1-6}$烷基、$-(CH_2)_q-$ 芳基、$-(CH_2)_q-$ 杂环基、$-(CH_2)_q-$ 环烷基、-OH、$-O-C_{1-6}$烷基、$-O-(CH_2)_q-$ 芳基、$-O-(CH_2)_q-$ 杂环基和 $-O-(CH_2)_q-$ 环烷基；

[0126] 或者 R^{28}和 R^{29}一起是=O、$-CH_2CH_2-$、$-CH_2CH_2CH_2-$ 或 $-CH_2CH_2CH_2CH_2-$；

[0127] p 是 1-4；

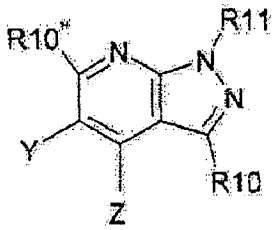
[0128] q 是 0-4；且

[0129] r 是 1-3；

[0130] 其中所述的芳基、杂环基和/或环烷基可以任选被一个或多个取代基 R^{27}取代。

[0131] WO2011/000566 的化合物具有通式 (XXI)：

[0132]



(XXI)

[0133] 或其药学上有效的盐、溶剂合物、前药、互变异构体、外消旋物、对映体或非对映体；

[0134] 其中

[0135] Y 和 Z 中的一个是 $-XR^{12}$且另一个是 $R^{10'}$；

[0136] R^{10}、$R^{10'}$和 $R^{10''}$各自独立地选自氢、C_1-C_6-烷基、C_2-C_6-烯基、C_2-C_8-炔基、$-(CH_2)$

$_n$C(O)OH、-$(CH_2)_n$C(O)OR^{16}、-$(CH_2)_n$OH、-$(CH_2)_n$$OR^{16}$、-$CF_3$、-$(CH_2)_n$- 环烷基、-$(CH_2)_n$C(O)$NH_2$、-$(CH_2)_n$C(O)$NHR^{16}$、-$(CH_2)_n$C(O)$NR^{16}R^{17}$、-$(CH_2)_n$S(O)$_2NH_2$、-$(CH_2)_n$S(O)$_2NHR^{16}$、-$(CH_2)_n$S(O)$_2NR^{16}R^{17}$、-$(CH_2)_n$S(O)$_2R^{16}$、卤素、-CN、-$(CH_2)_n$- 芳基、-$(CH_2)_n$- 杂芳基、-$(CH_2)_n$$NH_2$、-$(CH_2)_n$$NHR^{16}$和 -$(CH_2)_n$$NR^{16}R^{17}$;其是任选被取代的;

[0137] R^{11}选自氢、C_1-C_6- 烷基、-CF_3、C_2-C_6- 烯基、C_2-C_8- 炔基、-$(CH_2)_n$- 环烷基、-$(CH_2)_n$- 芳基、-$(CH_2)_n$- 杂环烷基和 -$(CH_2)_n$- 杂芳基;其是任选被取代的;

[0138] X 选自 CH_2、C(O)、C(S)、CH(OH)、$CH(OR^{16})$、$S(O)_2$、-$S(O)_2$-N(H)-、-$S(O)_2$-$N(R^{16})$-、-N(H)-$S(O)_2$-、-$N(R^{16})$-$S(O)_2$-、C(=NH)、$C(=N-R^{16})$、$CH(NH_2)$、$CH(NHR^{16})$、$CH(NR^{16}R^{17})$、-C(O)-N(H)-、-C(O)-$N(R^{16})$-、-N(H)-C(O)-、-$N(R^{16})$-C(O)-、N(H)、$N(-R^{16})$ 和 O;

[0139] R^{12}选自 C_1-C_6- 烷基、-CF_3、C_2-C_6- 烯基、C_2-C_8- 炔基、-$(CH_2)_n$- 环烷基、-$(CH_2)_n$- 杂环烷基、-$(CH_2)_n$- 芳基、-$NR^{16}R^{17}$和 -$(CH_2)_n$- 杂芳基;其是任选被取代的;

[0140] R^{16}和 R^{17}独立地选自 C_1-C_6- 烷基、C_2-C_6- 烯基、C_2-C_6- 炔基、-$(CH_2)_n$- 环烷基、-$(CH_2)_n$- 芳基、-CF_3、-C(O)R^{18}和 -$S(O)_2R^{18}$;其是任选被取代的;

[0141] R^{18}独立地选自 C_1-C_6- 烷基、C_2-C_6- 烯基、C_2-C_6- 炔基、-$(CH_2)_n$- 环烷基和 -CF_3;其是任选被取代的;且

[0142] n 在每种情况下选自 0、1 和 2。

[0143] 在 WO2011/000566 的上下文中,术语“任选被取代”在每种情况下指 1-10 个取代基,例如 1、2、3、4、5、6、7、8、9 或 10 个取代基,所述取代基在每种情况下优选独立地选自卤素,特别是 F、Cl、Br 或 I;-NO_2、-CN、-OR'、-NR'R″、-(CO)OR'、-(CO)OR'″、-(CO)NR'R″、-NR'COR‴、-NR'COR'、-NR″CONR'R″、-NR″SO_2A、-COR'″;-SO_2NR'R″、-OOCR'″、-CR'″R‴OH、-R‴OH、=O 和 -E;

[0144] R' 和 R″ 各自独立地选自氢、烷基、烯基、炔基、-OE、环烷基、杂环烷基、芳基、杂芳基和芳烷基,或者一起形成杂芳基或杂环烷基;其是任选被取代的;

[0145] R'″ 和 R‴ 各自独立地选自烷基、烯基、炔基、环烷基、杂环烷基、烷氧基、芳基、芳烷基、杂芳基和 -NR'R″;且

[0146] E 选自烷基、烯基、环烷基、烷氧基、烷氧基烷基、杂环烷基、脂环系、芳基和杂芳基;其是任选被取代的。

[0147] 在大流行病毒和季节性病毒二者中均出现了对两类获得许可的流感抗病毒药 (M2 离子通道抑制剂(金刚烷类)和神经氨酸酶抑制剂(奥塞米韦))的广泛抗药性,使得这些药物在治疗方式中仅具有最低限度的效用。对于 M2 离子通道抑制剂而言,病毒抗药性的频率自从 2003 年以来一直在增加,对于季节性流感 A/H3N2 而言,金刚烷类现在被认为是无效的。实际上,所有 2009H1N1 和季节性 H3N2 病毒株均对金刚烷类(金刚乙胺和金刚烷胺)具有抗药性,大部分季节性 H1N1 病毒株对奥塞米韦(最广泛被开具处方的神经氨酸酶抑制剂 (NAI))具有抗药性。就奥塞米韦而言,WHO 报告了在 2007/2008 流感季节开始的显著出现的流感 A/H1N1 抗药性;并且在南半球持续了 2008 年的第二和第三季度。在 2008 年的第四季度公开甚至更严重的数字(北半球),其中所有测试的分离物的 95% 显示对奥塞米韦不敏感。考虑到现在大多数国家的政府已经作为它们的流感大流行准备计划的一部分储备奥塞米韦的事实,显然对新的有效药物的需求大大增加。为了解决对更有效的疗法的需求,

已经用具有不同作用机制的抗病毒药的二联或甚至三联组合进行了初步研究。对金刚烷类和神经氨酸酶抑制剂的组合在体外和体内进行了分析，发现它们高度协同作用。然而，已知的是，非常迅速地出现了对这两类抗病毒药均有抗药性的病毒，这一问题无法通过组合使用这些已有的抗病毒药来解决。

[0148] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录活性的新药。针对病毒聚合酶的帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱病毒感染。这两个靶标位于聚合酶复合物的不同亚单位内，因此代表独特的药物靶标。由于两个功能都是所谓的“抢帽”机制（其是病毒转录所必须的）所需要的这一事实，预期同时抑制两种功能会高度协同地起作用。这种高度有效的药物组合将导致更低的物质浓度，并且因此导致改善的剂量－响应关系和更佳的副作用特性。

[0149] 在所有甲型流感病毒株（例如鸟和人）中这两个活性部位都由相同的残基构成，因此这种高度的序列保守性为这些靶标不可能引发迅速抗药病毒产生的认知提供了依据。因此，无论是何种病毒株，各自和组合使用的内切核酸酶和帽结合抑制剂是对抗季节性和大流行流感这二者的理想药物。

[0150] 内切核酸酶抑制剂和帽结合抑制剂的组合或靶向于内切核酸酶活性部位和帽结合结构域二者的双重特异性聚合酶抑制剂将有效对抗对金刚烷类和神经氨酸酶抑制剂有耐药性的病毒株，而且合并了对产生抗药性的低敏感性的优点与对宽范围的病毒株的活性。

[0151] (ii)不同抗病毒靶标的抑制剂的组合（特别是靶向于流感的）集中于作为双或多组合疗法的具有（优选流感）聚合酶抑制剂的组合。流感病毒聚合酶抑制剂是靶向于聚合酶转录活性的新药。针对病毒聚合酶得到帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱了病毒感染。预计特别针对病毒细胞内靶标的聚合酶抑制剂与不同抗病毒靶标的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药表现出完全不同的作用机制和有利地、协同地作用于所述组合的抗病毒功效的药物动力学性质。这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量－响应关系和更佳的副作用特性。此外，(i)项下针对聚合酶抑制剂所述的优点普遍存在于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合中。

[0152] 典型地，将选自第一组聚合酶抑制剂的至少一种化合物与选自第二组聚合酶抑制剂的至少一种化合物组合。

[0153] 能用于该类型的组合疗法的所述的第一组聚合酶抑制剂包括但不限于式(A)和/或(C)的化合物。

[0154] 能用于该类型的组合疗法的所述的第二组聚合酶抑制剂包括但不限于通式(I)的化合物、通式(II)的化合物、WO 2011/000566、WO 2010/110231、WO 2010/110409、WO 2006/030807或US 5,475,109中所公开的化合物以及flutimide及其类似物、法匹拉韦(favipiravir)及其类似物、表棓儿茶素棓酸酯(epigallocatechin gallate)及其类似物、以及核苷类似物例如利巴韦林。

[0155] (iii)聚合酶抑制剂与神经氨酸酶抑制剂的组合

[0156] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录活性的新药。针对病毒聚合酶的帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱病毒

感染。预计特异性地针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外抗病毒靶标、尤其是（例如病毒）神经氨酸酶的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药表现出完全不同的作用机制和有利地、协同地作用于所述组合的抗病毒功效的药物动力学性质。

[0157] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量－响应关系和更佳的副作用特性。此外，(i) 项下针对聚合酶抑制剂所述的优点普遍存在于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合中。

[0158] 典型地，将选自上述的第一组聚合酶抑制剂的至少一种化合物与至少一种神经氨酸酶抑制剂组合。

[0159] 对所述的神经氨酸酶抑制剂（特别是流感神经氨酸酶抑制剂）没有特别限制。实例包括扎那米韦、奥塞米韦、帕拉米韦 (peramivir)、KDNDANA、FANA 和环戊烷衍生物。

[0160] (iv) 聚合酶抑制剂与 M2 通道抑制剂的组合

[0161] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录活性的新药。针对病毒聚合酶的帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱病毒感染。预计特异性地针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外和细胞质抗病毒靶标、尤其是病毒 M2 离子通道的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药表现出完全不同的作用机制和有利地、协同地作用于所述组合的抗病毒功效的药物动力学性质。

[0162] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量－响应关系和更佳的副作用特性。此外，(i) 项下针对聚合酶抑制剂所述的优点普遍存在于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合中。

[0163] 典型地，将选自上述的第一组聚合酶抑制剂的至少一种化合物与至少一种 M2 通道抑制剂组合。

[0164] 对 M2 通道抑制剂（特别是流感 M2 通道抑制剂）没有特别限制。实例包括金刚烷胺和金刚乙胺。

[0165] (v) 聚合酶抑制剂与 α 葡糖苷酶抑制剂的组合

[0166] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录活性的新药。针对病毒聚合酶的帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱病毒感染。预计特异性地针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外靶标、尤其是 α 葡糖苷酶的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药表现出完全不同的作用机制和有利地、协同地作用于所述组合的抗病毒功效的药物动力学性质。

[0167] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量－响应关系和更佳的副作用特性。此外，(i) 项下针对聚合酶抑制剂所述的优点普遍存在于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合中。

[0168] 典型地，将选自上述的第一组聚合酶抑制剂的至少一种化合物与至少一种 α 葡糖苷酶抑制剂组合。

[0169] 对 α 葡糖苷酶抑制剂（特别是流感 α 葡糖苷酶抑制剂）没有特别限制。实例包括 Chang 等，Antiviral Research 2011, 89, 26-34 中所述的化合物。

[0170] (vi) 聚合酶抑制剂与其它流感靶标的配体的组合

[0171] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录活性的新药。针对病毒聚合酶的帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱病毒感染。预计特异性地针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外、细胞质或细胞核抗病毒靶标的抑制剂的组合高度协同地起作用。这基于以下事实:这些不同类型的抗病毒药表现出完全不同的作用机制和有利地、协同地作用于所述组合的抗病毒功效的药物动力学性质。

[0172] 这种高度有效的药物组合会导致更低的物质浓度,并且从而导致改善的剂量-响应关系和更佳的副作用特性。此外,(i) 项下针对聚合酶抑制剂所述的优点普遍存在于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合中。

[0173] 典型地,将选自上述的第一组聚合酶抑制剂的至少一种化合物与至少一种另外的流感靶标的配体组合。

[0174] 对另外的流感靶标的配体没有特别限制。实例包括作用于唾液酸酶融合蛋白的化合物,例如 Fludase(DAS181)、siRNA 和硫代磷酸寡核苷酸、信号转到抑制剂 (ErbB 酪氨酸激酶、Abl 激酶家族、MAP 激酶、PKCa- 介导的 ERK 信号发放的活化以及干扰素 (诱导物)。

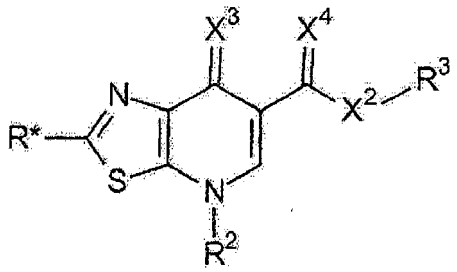
[0175] (vii)(优选流感) 聚合酶抑制剂与用作最小化疾病症状的辅药 (adjuvance) 的化合物 (抗生素、抗炎药如 COX 抑制剂 (例如 COX-1/COX-2 抑制剂、选择性 COX-2 抑制剂)、脂氧化酶抑制剂、EP 配体 (特别是 EP4 配体)、缓激肽配体和 / 或大麻素配体 (例如 CB2 激动剂) 的组合。流感病毒聚合酶抑制剂是靶向于聚合酶的转录活性的新药。针对病毒聚合酶的帽结合和内切核酸酶活性部位的选择性抑制剂通过停止病毒增殖周期而大幅度地减弱病毒感染。特异性地针对病毒细胞内靶标的聚合酶抑制剂与用作最小化疾病症状的辅药的化合物的组合解决了病毒感染的起因性和症状性病理结果。预计该组合协同地其作用,因为这些不同类型的药物表现出完全不同的作用机制和有利地、协同地作用于所述组合的抗病毒功效的药物动力学性质。

[0176] 这种高度有效的药物组合会导致更低的物质浓度,并且从而导致改善的剂量-响应关系和更佳的副作用特性。此外,(i) 项下针对聚合酶抑制剂所述的优点普遍存在于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合中。

[0177] 通式 (A) 的化合物

[0178] 下面给出了通式 (A) 的化合物。

[0179]



(A)

[0180] 本发明提供了通式 (A) 的化合物,其中适用下面的定义。

[0181] R*是 -H、-Hal、-(任选被取代的 C_{1-6} 烷基)、-(任选被取代的 C_{3-7} 环烷基)、-

（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的C_{3-7}环烷基）、-C_{1-4}烷基 -（任选被取代的芳基）或 -X^1-R^1。在一个优选的实施方案中，R^*是 -Hal、-（任选被取代的C_{1-6}烷基）（其中所述烷基的任选的取代基优选是Hal，更优选是F）；-C_{1-4}烷基 -（任选被取代的芳基）（其中所述芳基的任选的取代基优选是卤素）或 -X^1-R^1。在一个更优选的实施方案中，R* 是 X^1-R^1。

[0182] X^1是O、C(O)、C(O)O、OC(O)；S、SO、SO_2、NR^4、$N(R^5)C(O)$、$C(O)NR^5$，优选X^1是O或NR^4，更优选X^1是NR^4。在一个优选的实施方案中，X^1是NR^4且R^1和R^4结合在一起形成5-7元环，其可以任选含有O、S或还有N。在另一个优选的实施方案中，X^1是NR^4且R^1是 -SO_2-R^4。

[0183] X^2是O、S、NR^4，X^2优选是O。

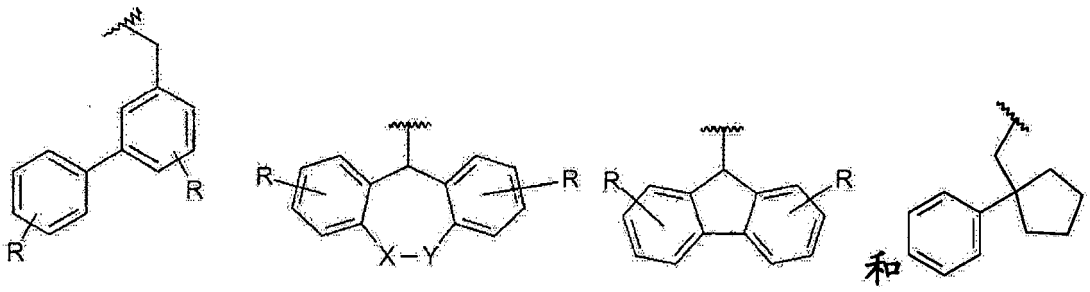
[0184] X^3是O或S，X^3优选是O。

[0185] X^4是O或S，X^4优选是O。

[0186] R^1是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的C_{3-7}环烷基）、-C_{1-4}烷基 -（任选被取代的芳基）。优选R^1是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的苄基），更优选R^1是 -H或-（任选被取代的苄基）。在本说明书中，应当理解的是，芳基的取代基定义类似地适用于苄基。

[0187] R^2是含有5-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的并且含有至少一个环的烃基，其中所述烃基可以是任选被取代的。优选地，所述的至少一个环是芳族的，例如芳基或杂芳基环。更优选地，R^2是含有5-20个碳原子并且任选含有1-4个杂原子的并且含有至少两个环的烃基，其中所述烃基可以是任选被取代的。甚至更优选地，所述的至少两个环中的至少一个环是芳族的，例如芳基或杂芳基环。R^2的优选的实例可以选自：

[0188]



[0189] 其中

[0190] X不存在、是CH_2、NH、C(O)NH、S或O。而且，

[0191] Y是CH_2。

[0192] 在一个供替代选择的实施方案中，X和Y可以结合在一起形成稠合的3-8元碳环或杂环，其可以是饱和的或不饱和的。X-Y的具体实例包括-CH_2-、-CH_2-CH_2-、-O-和-NH-。

[0193] R独立地选自H、-C_{1-6}烷基、卤素、-CN、-OH和 -O-C_{1-6}烷基。

[0194] R^3是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）或 -C_{1-4}烷基 -（任选被取代的芳基），如果X^2是NR^4，则R^3也可以是 -OH，优选地，R^3是 -H、-C_{1-6}烷基或Bz。

[0195] R^4是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的C_{3-7}环烷基）或 -C_{1-4}烷基 -（任选被取代的芳基），或者如果X^1是NR^4，则R^4和R^1可以结合在一起形成5-7元环，其可以任选含有O、S或还有N，或者如果X^2是NR^4，则R^4和R^3可以结合在一起形成5-7元环，其可以任选含有O、S或还有N。优选地，R^4是 -H、-（任选被取代的芳基）或 -（任选被取代的C_{1-6}烷基），更优选地，R^4是 -H或-（任选被取代的苄基）。

[0196] R^5是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）、-（任选被取代的芳基）、-C_{1-4}烷基 -（任选被取代的C_{3-7}环烷基）或 -C_{1-4}烷基 -（任选被取代的芳基）。优选地，R^5是 -H。

[0197] R^6是 -H或 -C_{1-6}烷基。

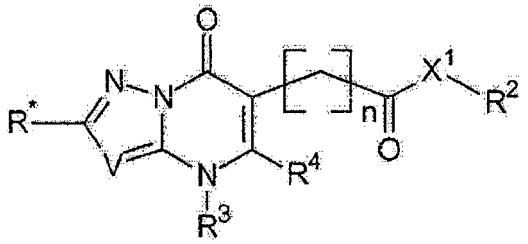
[0198] 所述的烷基的任选的取代基选自卤素、-CN、-NR^6R^6、-OH和 -O-C_{1-6}烷基。所述取代基优选是 - 卤素，更优选是F。

[0199] 所述的环烷基、芳基或烃基的任选的取代基选自 -C_{1-6}烷基、卤素、-CF_3、-CN、-X^1-R^5和 -C_{1-4}烷基 - 芳基。优选地，所述取代基是 - 卤素（优选F）、-OCH_3或-CN。

[0200] 通式(C)的化合物

[0201] 下面给出了通式(C)的化合物。

[0202]



(C)

[0203] 应当理解的是，在本申请文件中，除非另有说明，否则术语“通式(C)的化合物”涵盖药学上可接受的盐、溶剂合物、多晶型物、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物。

[0204] 在本发明中，就通式(C)的化合物而言，适用下面的定义。

[0205] V是N或CR^6。

[0206] X^1是O、S或NR^8，优选X^1是O。

[0207] X^2是NR^5、$N(R^5)C(O)$、$C(O)NR^5$、O、C(O)、C(O)O、OC(O)；S、SO、SO_2、$SO_2N(R^5)$或$N(R^5)SO_2$。优选地，X^2是NR^5或$N(R^5)SO_2$。

[0208] R^*是 -H、-Hal、-（任选被取代的C_{1-6}烷基）、-（任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团）、-C_{1-4}烷基 -（任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团）或 -X^2-R^1。优选地，R^*是H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的C_{3-7}环烷基）或 -X^2-R^1。

[0209] R^1是 -H、-（任选被取代的C_{1-6}烷基）、-（任选被取代的含有3-20个碳原子并且任选含有1-4个选自O、N和S的杂原子的单环或多环基团）、-C_{1-4}烷基 -（任选被

取代的含有 3 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的单环或多环基团）。优选地，R^1是 $-C_{1-4}$烷基 -（任选被取代的含有 3 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的单环或多环基团）。优选地，R^1是 $-C_{1-4}$烷基 -（任选被取代的含有 3 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的单环或多环基团）。

[0210] R^2是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、$-C_{1-4}$烷基 -（任选被取代的 C_{3-7}环烷基）或 $-C_{1-4}$烷基 -（任选被取代的芳基），或者如果 X^1是 NR'，则 R^2也可以是 -OH。优选地，R^2是 -H 或 $-C_{1-6}$烷基。

[0211] R^3是 -H、$-R^7$或 $-X^2-R^7$。优选地，R^3是 -H、$-C_{1-4}$烷基 -（任选被取代的芳基）或 $-SO_2-R^5$。优选地，R^3是 -H。

[0212] R^4是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、$-C_{1-4}$烷基 -（任选被取代的 C_{3-7}环烷基）或 $-C_{1-4}$烷基 -（任选被取代的芳基）。优选地，R^4是 -H 或 -（任选被取代的 C_{1-6}烷基）。

[0213] R^5是 -H、-（任选被取代的 C_{1-6}烷基）、-（任选被取代的 C_{3-7}环烷基）、-（任选被取代的芳基）、$-C_{1-4}$烷基 -（任选被取代的 C_{3-7}环烷基）或 $-C_{1-4}$烷基 -（任选被取代的芳基）。优选地，R^5是 $-C_{1-4}$烷基 -（任选被取代的芳基）或 -（任选被取代的 C_{3-7}环烷基）。

[0214] R^6是 H、$-C_{1-6}$烷基、- 芳基、卤素或 CN。优选地，R^6是 H 或 - 芳基。

[0215] R^7是 -（任选被取代的含有 5 - 20 个碳原子并且任选含有 1 - 4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基）。优选地，R^7是 $-C_{1-4}$烷基 -（任选被取代的芳基）。

[0216] R^8是 -H、$-C_{1-6}$烷基或 $-C_{1-4}$烷基 -（任选被取代的芳基）。优选地，R^8是 $-C_{1-6}$烷基或 $-C_{1-4}$烷基 -（任选被取代的芳基）。

[0217] n 是 0 - 4，优选是 0 或 1。

[0218] 所述的烷基的任选的取代基可以选自卤素、-CN、$-NR^5R^5$、-OH 和 $-O-C_{1-6}$烷基。

[0219] 所述的环烷基、芳基、单环或多环基团或者烃基的任选的取代基可以选自 $-C_{1-6}$烷基、卤素、$-CF_3$、-CN、$-X^2-C_{1-6}$烷基和 $-C_{1-6}$烷基 - 芳基。

[0220] 在不脱离本发明的范围的情况下本发明的各种调整和变型对于本领域技术人员而言是显而易见的。尽管已经使用具体的优选实施方案对本发明进行了描述，但是应当理解的是要求保护的发明不应当被不合理地局限于这些具体的实施方案。实际上，对于相关领域的技术人员而言显而易见的所述的实施本发明的方式的各种调整也被本发明所涵盖。

[0221] 下面的实施例仅用于对本发明进行举例说明，绝不应当理解为是对所附的权利要求所给出的本发明范围的限制。

实施例

[0222] FRET 内切核酸酶活性测定法

[0223] 如 Dias 等，Nature 2009；4 月 16 日；458(7240)，914-918 中所述的那样制备并纯化了具有流感内切核酸酶活性的甲型流感病毒 (IAV)PA-Nter 片段（氨基酸 1 - 209）。将该蛋白质溶解在含有 20mM Tris pH 8.0、100mM NaCl 和 10mM β - 巯基乙醇的缓冲液中，将等份试样贮存在 -20℃。

[0224] 将 20 个碱基的用 5′ -FAM 荧光团和 3′ -BHQ1 猝灭剂双重标记的 RNA oligo 作为通过 PA-Nter 的内切核酸酶活性裂解的底物。RNA 底物的裂解从猝灭剂中释放出荧光团，从而导致荧光信号增加。

[0225] 将所有测定组分稀释在含有 20mM Tris-HCl pH 8.0、100mM NaCl、1mM $MnCl_2$、10mM $MgCl_2$和 10mM β－巯基乙醇的测定缓冲液中。PA-Nter 的终浓度是 0.5μM 和 1.6μM RNA 底物。将测试化合物溶解在 DMSO 中，一般在两个浓度或者浓度系列下测试，从而使得最终的板孔 DMSO 浓度是 0.5%。在其中化合物在该浓度下不溶解的那些情况中，将它们在最高可溶的浓度下进行测试。在测定中用浓度为 0.1μM 的 SAV-6004 作为参比物。

[0226] 在一式八份的白色 384 孔微量滴定板 (PerkinElmer) 的孔中提供 5μl 每种化合物稀释液。加入 PA-Nter 稀释液后，将板密封并在室温下孵育 30min，然后加入 1.6μM 用测定缓冲液稀释的 RNA 底物。随后，在微量滴定板读数器 (Synergy HT, Biotek) 中在 485nm 的激发波长和 535nm 的发射波长下测量裂解的 RNA 的增加的荧光信号。动力学读数间隔是 35 秒，敏感度是 35。使用 20min 期间的荧光信号数据计算底物裂解的初始速度 (v0)。最终读数是与未处理的样品相比化合物处理的样品的 v0 的%降低。半数最大抑制剂浓度 (IC_{50}) 是化合物抑制生物学或生物化学功能的有效性量度，并且由最大 100μM－ 至少 2nM 范围内的给定浓度系列下的初始反应速度 (v0) 计算得到。

[0227] 细胞致病作用 (CPE) 测定法

[0228] 甲型流感病毒 (IAV) 获自美国组织培养物保藏中心 (American Tissue Culture Collection) (A/Aichi/2/68(H3N2) ;VR-547)。通过以下方法制备病毒储备液：在 Mardin-Darby 犬肾 (MDCK ;ATCC CCL-34) 细胞上繁殖病毒，如 Reed, L. J. 和 H. Muench. 1938, Am. J. Hyg. 27:493-497 中所述用 50%组织培养物感染剂量 ($TCID_{50}$) 分析测定病毒储备液的感染滴度。

[0229] 用含有 10%胎牛血清 (FBS)、2mM L-谷氨酰胺和 1%抗生素 (全部来自 PAA) 的 DMEM/Ham's F-12(1:1) 培养基将 MDCK 细胞以 2×10^4个细胞 / 孔接种在 96 孔板中。直至感染前，将细胞在 37℃、5.0% CO_2下孵育 5 小时，从而在孔的底部形成～ 80%汇合单层。将每种测试化合物溶解在 DMSO 中，一般在 25μM 和 250μM 下进行测试。在其中化合物在该浓度下不溶的那些情况中，将它们在最高可溶浓度下进行测试。将化合物稀释在感染培养基 (DMEM/Ham's F-12(1:1)，含有 5μg/ml 胰蛋白酶和 1%抗生素) 中，以便最终板孔 DMSO 浓度为 1%。将病毒储备液稀释在感染培养基 (DMEM/Ham's F-12(1:1)，含有 5μg/ml 胰蛋白酶、1% DMSO 和 1%抗生素) 中，以便理论感染复数 (MOI) 为 0.05。

[0230] 除去培养基并且用 PBS 进行一个洗涤步骤后，将病毒和化合物一起加入到孔中。在用于细胞毒性测定的孔中 (即，不存在病毒感染)，不加入病毒混悬液。代之以加入感染培养基。每个处理均一式两份地进行。在 37℃、5% CO_2下孵育 48 小时后，用显微镜观察每个孔的表观细胞毒性、沉淀物形成或其它值得注意的异常。然后，用 CellTiter-Glo 发光细胞生存力测定法 (Promega) 测定细胞生存力。小心地取出上清液，向每个孔中加入 65μl 重构的试剂，在温和振摇下于室温孵育 15min。然后，将 60μl 溶液转移到不透明的板中，用 Synergy HT 板读数器 (Biotek) 测量发光 (RLU)。

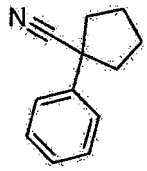
[0231] 用与未感染的未处理的细胞相比的未感染的处理的细胞的相对细胞生存力值评价化合物的细胞毒性。将在测试浓度下相对生存力低于 80%的物质视为是细胞毒性的，在

更低浓度下再进行测试。

[0232] 如下计算经化合物处理的病毒介导的细胞致病作用 (CPE) 的降低 :从感染的处理的样品的响应 (RLU) 中减去感染的未处理的样品的响应 (RLU),然后用相应的未感染的样品的生存力归一化,得到% CPE 降低。半数最大抑制浓度 (IC_{50}) 是化合物抑制生物学或生物化学功能的有效性的量度,是由最大 100 μM - 至少 100nM 范围内的给定浓度系列的 RLU 响应计算得到的。

[0233] 实施例 1 :1- 苯基 - 环戊烷甲腈的制备

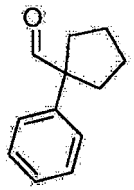
[0234]



[0235] 在 0 ℃下向 NaH(11.3g,281.7mmol,60 %) 在 DMSO(75ml) 中的混悬液中滴加溶于 DMSO: 乙醚 (150ml,1:1) 的苯基 - 乙腈 (15g,128.0mmol) 和 1,4- 二溴 - 丁烷 (18ml,128.0mmol) 的混合物,将反应混合物在室温 (RT) 搅拌 2-3h。反应完全后,向粗品物料中加入水和 10% HCl 溶液。将其用 EtOAc 萃取。用 Na_2SO_4 干燥有机层,浓缩,通过柱色谱法 (10% EtOAc- 己烷) 纯化,得到 1- 苯基 - 环戊烷甲腈 (2)(19g,86.64%),为黄色固体。MS :m/z = 171(MH+)。

[0236] 实施例 2 :1- 苯基 - 环戊烷甲醛的制备

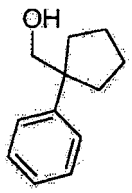
[0237]



[0238] 向 1- 苯基 - 环戊烷甲腈 (17g,99.4mmol) 在 DCM(200ml) 中的溶液中非常缓慢地加入氢化二异丁基铝 (DIBAL)(140ml,25%的甲苯溶液,248.5mmol)。将该混合物在 - 70℃搅拌 2h。反应完全后,通过添加酒石酸钾钠溶液将其缓慢地猝灭,然后将该混合物在 RT 搅拌 16h。然后将其用二氯甲烷 (DCM) 萃取,用水、盐水洗涤,用 Na_2SO_4 干燥。浓缩有机相,得到 1- 苯基 - 环戊烷甲醛,为无色液体 (15.5g, 粗品)。

[0239] 实施例 3 :(1- 苯基 - 环戊基)- 甲醇的制备

[0240]

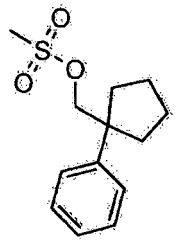


[0241] 将 $NaBH_4$(3.2g,86.2mmol) 分份加入到冷却的 (冰浴)1- 苯基 - 环戊烷甲醛 (7.5g,43.1mmol) 在甲醇 (100ml) 中的溶液中,然后在 RT 搅拌 16h。反应完全后,将其在减压下用饱和氯化铵溶液和甲醇猝灭。用水稀释该混合物,用 EtOAc 萃取,用水、盐水洗涤,干燥 (Na_2SO_4),减压蒸发至干。进行色谱处理 (15% EtOAc 的己烷溶液),得到 (1- 苯基 - 环

戊基)-甲醇,为白色固体(6g,79.8%)。

[0242] 实施例4:甲磺酸1-苯基-环戊基甲酯的制备

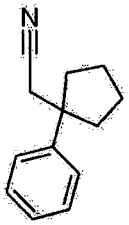
[0243]



[0244] 向(1-苯基-环戊基)-甲醇(11.5g,64.34mmol)在DCM(100ml)中的溶液中加入TEA(17.5ml,130.68mmol),然后在0℃滴加甲磺酰氯(MsCl)(8.9g,78.4mmol),将反应混合物在RT搅拌16h。反应完全后,将其用水猝灭并浓缩。然后将粗产物溶于DCM,用DCM萃取,用水和盐水洗涤有机层,然后用Na_2SO_4干燥。浓缩合并的有机层,得到粗品甲磺酸1-苯基-环戊基甲酯(10g,粗品),为白色固体。

[0245] 实施例5:(1-苯基-环戊基)-乙腈的制备

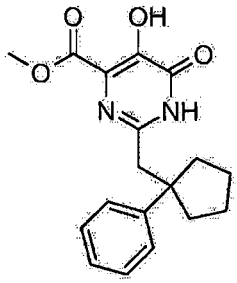
[0246]



[0247] 向搅拌着的甲磺酸1-苯基-环戊基甲酯(10g,39.37mmol)在DMSO(30ml)中的溶液中加入KI(0.6g,3.9mmol)和NaCN(2.89g,59.05mmol)。然后将其在140℃搅拌16h。反应完全后,将其用水稀释,用EtOAc萃取,用水和盐水洗涤有机层。然后将其用Na_2SO_4干燥,浓缩,通过正相柱色谱法(15% EtOAc的己烷溶液)纯化,得到标题化合物,为无色液体(2.5g,34%)。

[0248] 实施例6:5-羟基-6-氧代-2-(1-苯基-环戊基甲基)-1,6-二氢-嘧啶-4-甲酸甲酯的制备

[0249]

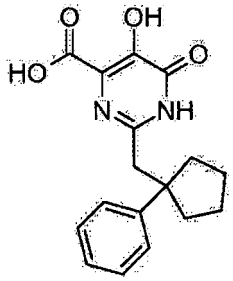


[0250] 将氢氧化钾(10.8ml,10.8mmol)的甲醇溶液与盐酸羟胺(10.8ml,10.8mmol)的甲醇溶液混合,过滤,加入到2-(1-苯基环戊基)乙腈(1g,5.4mmol)的甲醇(MeOH)溶液中,在60℃搅拌24h。然后将其蒸发至干。将残余物溶于氯仿(30ml),向其中加入丁-2-炔二酸二甲酯(dimethyl but-2-ynedioate)(844mg,5.94mmol)。将反应混合物在60℃搅拌24h,

冷却，蒸发至干。将残余物溶于二甲苯 (10ml)，于 140℃在微波炉中加热 1h。将冷却的残余物蒸发至干。进行色谱处理 (40g SiO_2;10-70％ EtOAc 的己烷溶液)。将残余物与 EtOAc 一起研磨，过滤，用 Et_2O 洗涤，真空干燥，得到标题产物，为灰白色固体 (0.110g ;6％). LCMS : m/z ＝ 329(MH+)。

[0251] 实施例 7 :5- 羟基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸的制备

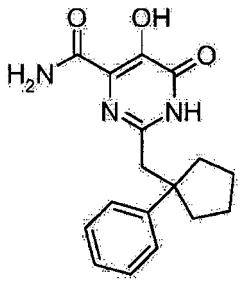
[0252]



[0253] 将氢氧化锂 (7.66mg,320 μ mol) 在水 (1.00ml) 中的溶液加入到搅拌着的 5,6- 二羟基 -2-((1- 苯基环戊基) 甲基) 嘧啶 -4- 甲酸甲酯 (0.035g,107 μ mol) 在四氢呋喃 (THF) (4ml) 中的混合物中。将该混合物在 RT 搅拌 72h，然后用 amberlyst(H+) IE 树脂猝灭，过滤，蒸发至干。将残余物与 EtOAc 一起研磨，真空干燥，得到标题产物，为白色固体 (0.012g ; 32％). LCMS :m/z ＝ 315(MH+)。

[0254] 实施例 8 :5- 羟基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酰胺的制备

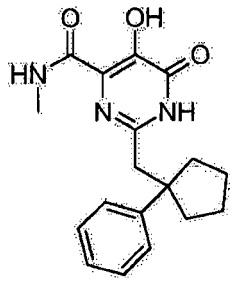
[0255]



[0256] 将 5,6- 二羟基 -2-((1- 苯基环戊基) 甲基) 嘧啶 -4- 甲酸甲酯 (0.020g,60.9 μ mol) 在氨的 MeOH 溶液 (435 μ l,3.05mmol) 中的溶液在 100℃加热 20min。将冷却的溶液蒸发至干。用 MeOH 稀释残余物，在 Amberlyst 树脂 (H+) 的存在下加热至形成溶液。过滤物料以除去树脂，蒸发至干。与 MeOH 一起研磨，然后用 Et_2O 洗涤，得到所需的产物，为白色固体 (0.011g ;49％)。LCMS :m/z ＝ 314(MH+)。

[0257] 实施例 9 :5- 羟基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

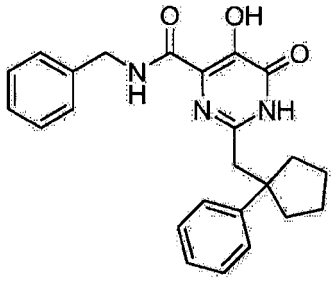
[0258]



[0259] 在氮气气氛下在微波容器中向5,6-二羟基-2-(1-苯基-环戊基甲基)-嘧啶-4-甲酸甲酯(55mg,0.167mmol)在THF(2ml)中的溶液中加入2M甲胺的THF溶液(0.419mL,0.838mmol)。将反应混合物在微波炉中于110℃加热10min,然后冷却,蒸发至干。用水和30%乙酸乙酯的己烷溶液洗涤残余物,得到标题化合物,为灰白色固体(0.020g,36%)。LCMS :m/z = 327.8(MH+)。

[0260] 实施例10:5-羟基-6-氧代-2-(1-苯基-环戊基甲基)-1,6-二氢-嘧啶-4-甲酸苄基酰胺的制备

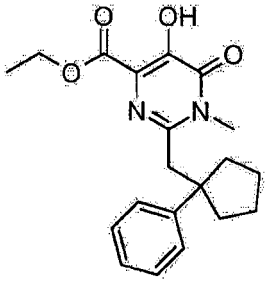
[0261]



[0262] 按照针对5-羟基-6-氧代-2-(1-苯基-环戊基甲基)-1,6-二氢-嘧啶-4-甲酸甲基酰胺(实施例9)所述的操作由55mg 5,6-二羟基-2-(1-苯基-环戊基甲基)-嘧啶-4-甲酸甲酯合成了5,6-二羟基-2-(1-苯基-环戊基甲基)-嘧啶-4-甲酸苄基酰胺,为灰白色固体(20mg,30%)。LCMS :m/z = 403.8(MH+)。

[0263] 实施例11:5-羟基-1-甲基-6-氧代-2-(1-苯基-环戊基甲基)-1,6-二氢-嘧啶-4-甲酸乙酯的制备

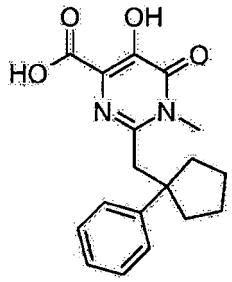
[0264]



[0265] 按照针对5-羟基-6-氧代-2-(1-苯基-环戊基甲基)-1,6-二氢-嘧啶-4-甲酸甲酯(实施例6)所述的操作由200mg 5-乙氧基羰基甲基-2-甲基-3-(1-苯基-环戊基甲基)-2,5-二氢-[1,2,4]噁二唑-5-甲酸乙酯合成了5-羟基-1-甲基-6-氧代-2-(1-苯基-环戊基甲基)-1,6-二氢-嘧啶-4-甲酸乙酯,为棕色固体(35mg,20%)。LCMS :m/z = 357.0(MH+)。

[0266] 实施例 12 :5- 羟基 -1- 甲基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸的制备

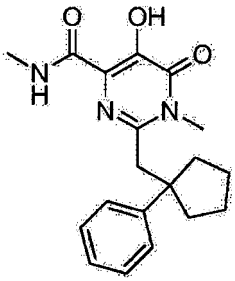
[0267]



[0268] 按照针对 5- 羟基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸 (实施例 7) 所述的操作由 140mg 5- 羟基 -1- 甲基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸乙酯合成了 5- 羟基 -1- 甲基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸乙酸,为白色固体 (30mg,23.2%)。LCMS :m/z 327.0(M-H)。

[0269] 实施例 13 :5- 羟基 -1- 甲基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

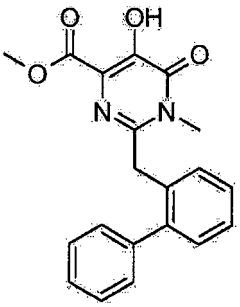
[0270]



[0271] 在氩气气氛下在密封试管中向 5- 羟基 -1- 甲基 -6- 氧代 -2-(1- 苯基 - 环戊基甲基)-1,6- 二氢 - 嘧啶 -4- 甲酸乙酯 (175mg,0.491mmol) 和甲胺 (0.98ml,1.96mmol,2M 的 THF 溶液) 的混合物中加入催化量的 Me_3Al,将其在 60℃加热 16h。反应完全后,将其用冰缓慢地猝灭,然后用 EtOAc 萃取。然后用水和盐水洗涤合并的有机层。然后将其用 Na_2SO_4 干燥,真空浓缩。通过制备型 HPLC 纯化,得到标题化合物,为灰白色固体 (40mg,24%)。LCMS : m/z = 342.0(MH+)。

[0272] 实施例 14 :2- 联苯 -2- 基甲基 -5- 羟基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

[0273]

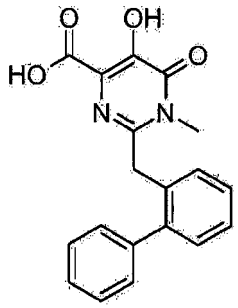


[0274] 将含有 2-(联苯 -2- 基) 乙腈 (2g,10.3mmol)、碳酸钠 (329mg,3.1mmol) 和 N- 甲

基羟胺盐酸盐 (432mg, 5.17mmol) 在乙醇 (5ml) 和水 (5ml) 中的混合物在 80℃加热 2h，冷却，用丁 -2- 炔二酸二甲酯 (809mg, 5.69mmol) 处理。将该混合物在室温搅拌 5h，然后用 EtOAc 稀释，用水和盐水洗涤，干燥 ($MgSO_4$)，蒸发至干。进行色谱处理 (40g SiO_2, 10-60% EtOAc 的己烷溶液)，得到 1, 2, 4- 噁二唑啉中间体，为橙色油状物。用二甲苯 (5.00ml) 稀释该油状物，于 130℃在微波炉中加热 3.5h。用 EtOAc 稀释冷却的混合物，用盐水洗涤，干燥 ($MgSO_4$)，蒸发至干。进行色谱处理 (24g SiO_2;20-60% EtOAc 的己烷溶液)，得到标题化合物，为淡棕色泡沫 (0.43g ;81%)。LCMS :m/z = 351(MH+)。

[0275] 实施例 15 :2- 联苯 -2- 基甲基 -5- 羟基 -1- 甲基 -6- 氧代 -1, 6- 二氢 - 嘧啶 -4- 甲酸的制备

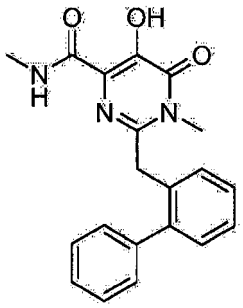
[0276]



[0277] 将氢氧化锂 (8.2mg, 342 μmol) 在水中的溶液加入到搅拌着的 2-(联苯 -2- 基甲基)-5- 羟基 -1- 甲基 -6- 氧代 -1, 6- 二氢嘧啶 -4- 甲酸甲酯 (0.1g, 285 μmol) 在 THF 中的溶液中。24h 后，通过添加 1M HCl 猝灭反应，萃取入 EtOAc 中，用盐水洗涤，干燥 ($MgSO_4$)，蒸发。通过制备型 HPLC 纯化，得到所需的产物，为白色固体 (0.010g ;10%)。LCMS :m/z = 337(MH+)。

[0278] 实施例 16 :2- 联苯 -2- 基甲基 -5- 羟基 -1- 甲基 -6- 氧代 -1, 6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

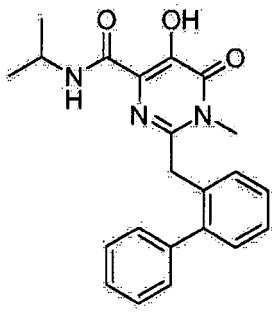
[0279]



[0280] 将含有 2M 甲胺 (1.71ml, 3.42mmol) 在 THF 中的溶液和 2-(联苯 -2- 基甲基)-5- 羟基 -1- 甲基 -6- 氧代 -1, 6- 二氢嘧啶 -4- 甲酸甲酯 (0.1g, 285 μmol) 的密封试管于 100℃在微波炉中加热 20min，冷却，过滤。将固体在 MeOH 中在 Amberlyst 15IE 树脂的存在下于 60℃搅拌 5min，然后在室温搅拌 1h，过滤，蒸发至干，与 Et_2O 一起研磨，得到标题化合物，为白色固体 (0.040g ;40%)。LCMS :m/z = 351(MH+)。

[0281] 实施例 17 :2- 联苯 -2- 基甲基 -5- 羟基 -1- 甲基 -6- 氧代 -1, 6- 二氢 - 嘧啶 -4- 甲酸异丙基酰胺的制备

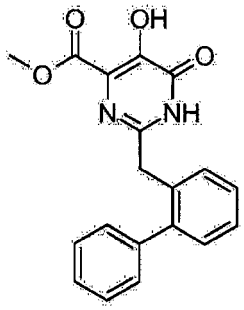
[0282]



[0283] 将含有丙烷-2-胺(202mg,292μl,3.42mmol)、2-(联苯-2-基甲基)-5-羟基-1-甲基-6-氧代-1,6-二氢嘧啶-4-甲酸甲酯(0.1g,285μmol)和THF(1.7ml)的密封试管于100℃在微波炉中加热20分钟。冷却粗品反应混合物,蒸发至干。通过制备型HPLC纯化,得到所需的产物,为淡粉色固体(0.015g;14%)。LCMS:m/z = 379(MH+)。

[0284] 实施例18:2-联苯-2-基甲基-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸甲酯的制备

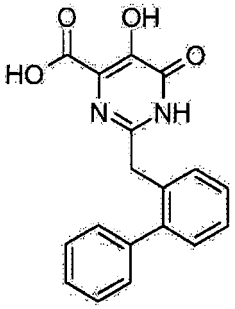
[0285]



[0286] 在0℃合并1M盐酸羟胺在MeOH中的溶液(15ml)和1M KOH的MeOH溶液(15ml)。10分钟后,通过过滤除去盐,将滤液直接加入到含有2-(联苯-2-基)乙腈(0.50g,2.58mmol)的烧瓶中,在60℃加热过夜。将冷却的混合物减压蒸发至干,将残余物溶于EtOAc,用水和盐水洗涤,干燥($MgSO_4$),蒸发至干。将残余物溶于氯仿(10ml),用丁-2-炔二酸二甲酯(0.403g,2.84mmol)处理。将该混合物在60℃搅拌1h,然后蒸发至干。用二甲苯(10ml)稀释残余物,在130℃加热90min。过滤冷却的滤液,与EtOAc一起研磨,真空干燥,得到标题产物,为灰白色固体(0.161g;18%)。LCMS:m/z = 337(MH+)。

[0287] 实施例19:2-联苯-2-基甲基-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸的制备

[0288]

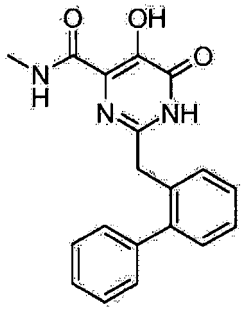


[0289] 根据实施例15使用2-联苯-2-基甲基-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲

酸甲酯 (0.050g ;0.148mmol) 制备了标题产物。标题化合物以灰白色固体形式被制备 (0.020g ;41%)。LCMS :m/z = 321(M-H)。

[0290] 实施例 20 :2- 联苯 -2- 基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

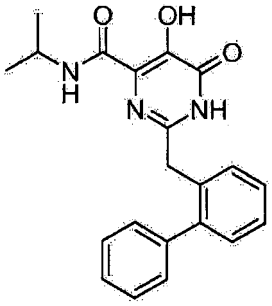
[0291]



[0292] 将含有 2M 甲胺 (2ml,4mmol) 的 THF 溶液和 2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.05g,163 μ mol,Eq :1.00) 的密封试管于 150℃在微波炉中加热 15min,冷却,过滤。将固体在 MeOH 中在 Amberlyst 15IE 树脂的存在下于 60℃搅拌 5min,然后在室温搅拌 1h,过滤,蒸发至干,与 Et_2O 一起研磨,得到标题化合物,为白色固体 (0.015g ;27%)。LCMS :m/z = 336(MH+)。

[0293] 实施例 21 :2- 联苯 -2- 基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸异丙基酰胺的制备

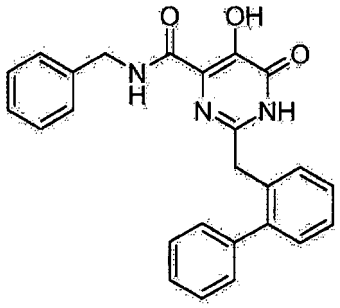
[0294]



[0295] 将含有丙烷 -2- 胺 (347mg,500 μ l,5.87mmol)、2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.50g,148 μ mol) 的密封试管于 150℃在微波炉中加热 10 分钟。冷却粗品反应混合物,蒸发至干。将固体残余物在 MeOH 中在 Amberlyst 15IE 树脂的存在下于 60℃搅拌 5min,然后在室温搅拌 1h,过滤,蒸发至干,与 Et_2O 一起研磨,得到标题化合物,为白色固体 (0.012g ;22%). LCMS :m/z = 364(MH+)。

[0296] 实施例 22 :2- 联苯 -2- 基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸苄基酰胺的制备

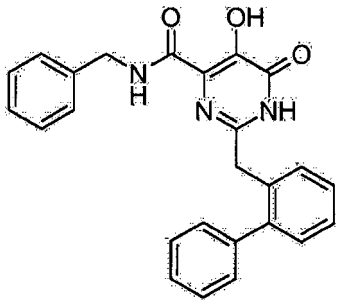
[0297]



[0298] 如实施例 21 中所述使用 2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.070g,208μmol) 和苄基胺 (0.5ml ;4.58mmol) 进行合成,得到标题化合物,为灰白色固体 (0.055g ;64%). LCMS :m/z = 412(MH+)。

[0299] 实施例 23 :2- 联苯 -2- 基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸 -4- 氟苄基酰胺的制备

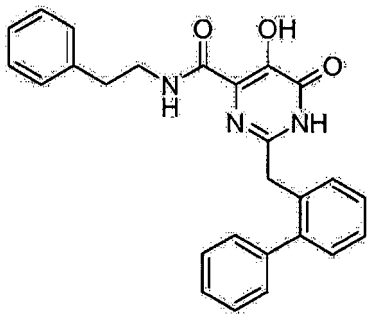
[0300]



[0301] 如实施例 21 中所述使用 2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.070g,208μmol) 和 4- 氟苄基胺 (0.5ml ;4.38mmol) 进行合成,得到标题化合物,为灰白色固体 (0.016g ;18%)。LCMS :m/z = 430(MH+)。

[0302] 实施例 24 :2- 联苯 -2- 基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸苯乙基酰胺的制备

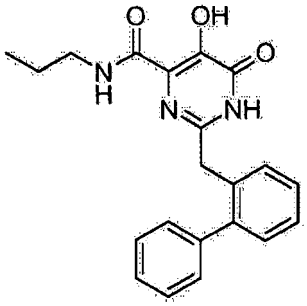
[0303]



[0304] 如实施例 21 中所述使用 2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.10g,298μmol) 和苯乙胺 (0.5ml ;3.98mmol) 进行合成,得到标题化合物,为灰白色固体 (0.054g ;42%)。LCMS :m/z = 425(MH+)。

[0305] 实施例 25 :2- 联苯 -2- 基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸异丙基酰胺的制备

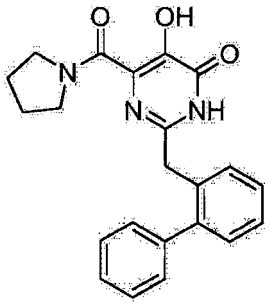
[0306]



[0307] 如实施例 21 中所述使用 2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.10g,298μmol) 和异丙基胺 (0.5ml ;6.10mmol) 进行合成,得到标题化合物,为灰白色固体 (0.059g ;54%)。LCMS :m/z = 412(MH+)。

[0308] 实施例 26 :2- 联苯 -2- 基甲基 -5- 羟基 -6-(吡咯烷 -1- 羰基)-3H- 嘧啶 -4- 酮的制备

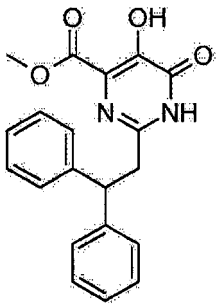
[0309]



[0310] 如实施例 21 中所述使用 2-(联苯 -2- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.10g,298μmol) 和吡咯烷 (0.5ml ;6.06mmol) 进行合成,得到标题化合物,为灰白色固体 (0.059g ;54%)。LCMS :m/z = 412(MH+)。LCMS :m/z = 375(MH+)。

[0311] 实施例 27 :2-(2,2- 二苯基 - 乙基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

[0312]

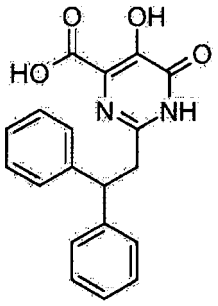


[0313] 在 0 ℃ 将盐酸羟胺 (38.6ml,38.6mmol) 的 MeOH 溶液加入到氢氧化钾 (38.6ml,38.6mmol,Eq :4) 的 MeOH 溶液中。过滤得到的混合物,将滤液加入到含有 3,3- 二苯基丙腈 (2g,9.65mmol) 的 150mL 圆底烧瓶中。将该混合物在回流下加热 16h,冷却,蒸发至干。将残余物溶于 EtOAc,用盐水洗涤,干燥 ($MgSO_4$),蒸发至干。将粗产物溶于 $CHCl_3$(50ml),用丁 -2- 炔二酸二甲酯 (1.65g,11.6mmol,Eq :1.2) 处理,在回流下加热 1h,然后蒸发至干。将残余物溶于二甲苯 (10ml),于 120℃在微波炉中加热 4h,蒸发至干。进行色谱处理 (80g SiO_2;20-100% EtOAc 的己烷溶液),得到标题产物,为灰白色固体 (0.42 ;12%)。LCMS :m/

z = 348.9(MH+)。

[0314] 实施例 28 :2-(2,2- 二苯基 - 乙基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸的制备

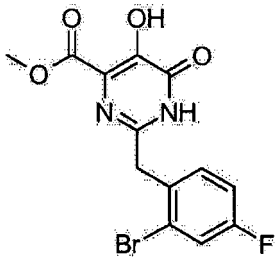
[0315]



[0316] 将氢氧化锂 (21.9mg,913μmol) 在水 (2ml) 中的溶液加入到含有搅拌着的 2-(2,2- 二苯基 - 乙基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯 (0.160g,457μmol) 在 THF(8ml) 中的溶液的烧瓶中。将该混合物在室温搅拌 8h,用 1M HCl 猝灭,萃取入 EtOAc 中,用盐水洗涤,干燥 ($MgSO_4$),蒸发至干。通过制备型 HPLC 纯化,得到所需的产物,为白色固体 (0.024g ;15%)。LCMS :m/z = 337(MH+)。

[0317] 实施例 29 :2-(2- 溴 -4- 氟 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

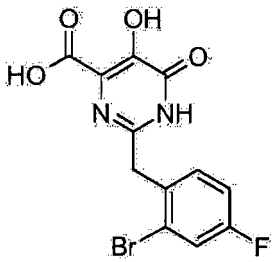
[0318]



[0319] 将氢氧化钾 (18.7ml,18.7mmol) 的甲醇溶液与盐酸羟胺 (18.7ml,18.7mmol) 的甲醇溶液混合,过滤,加入到 2-(2- 溴 -4- 氟苯基) 乙腈 (1g,4.67mmol) 的 MeOH 溶液中,在 60℃搅拌 24h,蒸发至干。将残余物溶于氯仿 (30.0ml),向其中加入丁 -2- 炔二酸二甲酯 (730mg,5.14mmol)。将该混合物在 60℃搅拌 24h,冷却,蒸发至干。将残余物溶于二甲苯 (10ml),于 120℃在微波炉中加热 2h。将冷却的残余物蒸发至干,然后与 EtOAc 一起研磨,过滤,用 Et_2O 洗涤,得到标题化合物,为棕色固体 (0.21g ;12%)。LCMS :m/z = 358(MH+)。

[0320] 实施例 30 :2-(2- 溴 -4- 氟 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸的制备

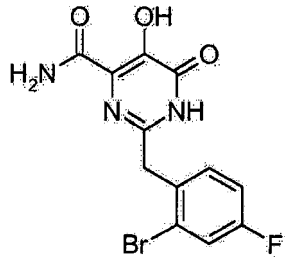
[0321]



[0322] 将氢氧化锂一水合物 (23.5mg,560μmol) 在水 (1ml) 中的溶液加入到搅拌着的 2-(2- 溴 -4- 氟苄基)-5,6- 二羟基嘧啶 -4- 甲酸甲酯 (50mg,140μmol) 在 THF(4ml) 中的溶液中。将得到的混合物在室温搅拌 24h。然后通过添加 Amberlyst 树脂酸化该混合物,过滤,蒸发至干。将残余物与 Et_2O 一起研磨,得到标题化合物,为白色固体 (0.02g ;41%)。LCMS :m/z = 344(MH+)。

[0323] 实施例 31 :2-(2- 溴 -4- 氟 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酰胺的制备

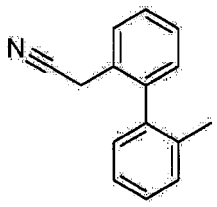
[0324]



[0325] 将氨的 MeOH 溶液 (1mL,7.00mmol) 加入到含有 2-(2- 溴 -4- 氟苄基)-5,6- 二羟基嘧啶 -4- 甲酸甲酯 (50mg,140μmol) 的烧瓶中。将该混合物于 120℃在微波炉中加热 15 分钟。通过过滤收集得到的产物,与 Amberlyst 树脂一起混悬于 MeOH 中,加热。过滤温热的混合物,蒸发至干。将残余物与 Et_2O 一起研磨,真空干燥,得到标题化合物,为白色固体 (0.032g ;67%)。LCMS :m/z = 343(MH+)。

[0326] 实施例 32 :(2' - 甲基 - 联苯 -2- 基)- 乙腈的制备

[0327]

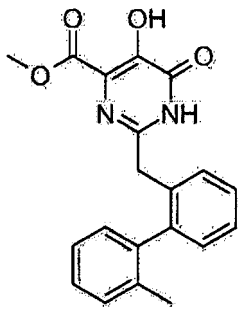


[0328] 在小瓶中,将 2- 溴苯基乙腈 (2g,10.2mmol)、2- 甲基苯基硼酸 (1.53g,11.2mmol) 和碳酸钾 (2.82g,20.4mmol,Eq :2) 与甲苯 (15.0ml)、乙醇 (15ml) 和水 (5ml) 合并,得到淡棕色混悬液。用氩气给该混合物脱气,然后加入四 (三苯膦) 钯 (0)(354mg,306μmol)。将反应混合物在 90℃加热 12h,冷却,倾入水中,用 EtOAc 萃取。用盐水洗涤有机相,干燥 (Na_2SO_4),减压蒸发至干。进行色谱处理 (硅胶 ,0% -5% EtOAc 的己烷溶液),得到标题产物,为无色油状物 (1.57g ;74%)。

[0329] ^1H NMR(300MHz ;$CDCl_3$) δ ppm 2.06(s,3H),3.43(s,2H),7.07-7.61(m,8H).

[0330] 实施例 33 :5- 羟基 -2-(2' - 甲基 - 联苯 -2- 基甲基)-6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

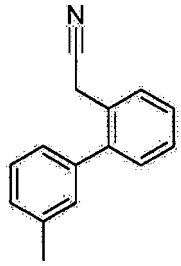
[0331]



[0332] 在 0℃将盐酸羟胺 (979mg, 14.1mmol) 在甲醇 (15ml) 中的溶液和氢氧化钾 (790mg, 14.1mmol) 在甲醇 (15ml) 中的溶液合并，通过过滤除去固体 (KCl)。将滤液加入到 2-(2'-甲基联苯-2-基) 乙腈 (1.46g, 7.04mmol) 中，在 60℃加热过夜。再加入 1 当量的 NH_2OH 的 MeOH 溶液，持续加热 5h。冷却该混合物，然后真空浓缩。将残余物用 $CHCl_3$(30ml) 吸收，向其中加入乙炔二甲酸二甲酯 (1.00g, 7.04mmol)。将该混合物在 60℃加热过夜，冷却，蒸发。将残余物转入微波小瓶中，加入二甲苯 (8ml)。封盖小瓶，在微波炉中于 140℃加热 3h，冷却。进行色谱处理 (硅胶；10% -100% EtOAc 的己烷溶液)，得到所需的产物，为灰白色固体 (0.003g；0.12%)。LCMS：m/z = 351(MH+)。

[0333] 实施例 34：(3'-甲基-联苯-2-基)-乙腈的制备

[0334]

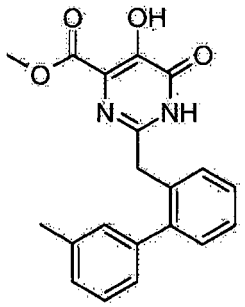


[0335] 在小瓶中，将 2-溴苯基乙腈 (2g, 10.2mmol)、间-甲苯基硼酸 (1.66g, 12.2mmol) 和碳酸钾 (2.82g, 20.4mmol) 与甲苯 (15ml)、乙醇 (15ml) 和水 (5ml) 合并，得到淡棕色混悬液。用氩气给该混合物脱气，然后加入四 (三苯膦) 钯 (0)(354mg, 306μmol)。将反应混合物加热至 90℃，搅拌过夜。用水稀释得到的冷却的混合物，萃取入 EtOAc 中。分离有机相，用盐水洗涤，干燥 (Na_2SO_4)，减压浓缩。进行色谱处理 (硅胶，0% -5% EtOAc 的己烷溶液)，得到标题产物，为无色油状物 (1.82g；80%)。

[0336] ^1H NMR(300MHz；$CDCl_3$) δ ppm 2.42(s, 3H), 3.65(s, 2H), 7.03-7.62(m, 8H).

[0337] 实施例 35：5-羟基-2-(3'-甲基-联苯-2-基甲基)-6-氧代-1,6-二氢-嘧啶-4-甲酸甲酯的制备

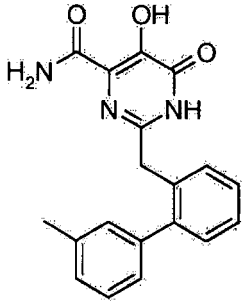
[0338]



[0339] 利用与实施例32中相同的通用操作使用2-(3'-甲基联苯-2-基)乙腈(1.81g,8.73mmol)制备了该化合物。分离标题产物,为白色固体(0.07g;2%)。LCMS:m/z=351(MH+)。

[0340] 实施例36:5-羟基-2-(3'-甲基-联苯-2-基甲基)-6-氧代-1,6-二氢-嘧啶-4-甲酰胺的制备

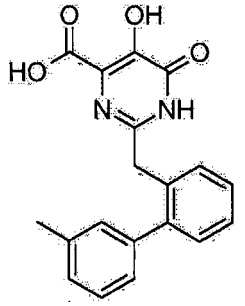
[0341]



[0342] 将含有5-羟基-2-((3'-甲基联苯-2-基)甲基)-6-氧代-1,6-二氢嘧啶-4-甲酸甲酯(55mg,157μmol)和氨(7M的MeOH溶液)(4ml,28.0mmol)在MeOH(2ml)中的混合物在100℃加热过夜。真空浓缩冷却的反应混合物,然后在甲醇中研磨,得到标题产物,为灰白色固体(0.025g;47%)。LCMS:m/z=336(MH+)。

[0343] 实施例37:5-羟基-2-(3'-甲基-联苯-2-基甲基)-6-氧代-1,6-二氢-嘧啶-4-甲酸的制备

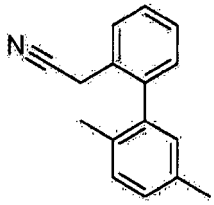
[0344]



[0345] 在圆底烧瓶中,将5-羟基-2-((3'-甲基联苯-2-基)甲基)-6-氧代-1,6-二氢嘧啶-4-甲酸甲酯(30mg,85.6μmol)和氢氧化锂水合物(6.5mg,155μmol)与THF(2ml)和水(1ml)合并,得到无色溶液。将该混合物在50℃搅拌1天。加入Amberlyst(15,离子交换树脂),将该混合物搅拌10min,过滤,蒸发至干。与EtOAc和己烷一起研磨,得到标题化合物,为白色固体(0.011g;34%)。LCMS:m/z=337(MH+)90%纯度。

[0346] 实施例38:(2',5'-二甲基-联苯-2-基)-乙腈的制备

[0347]

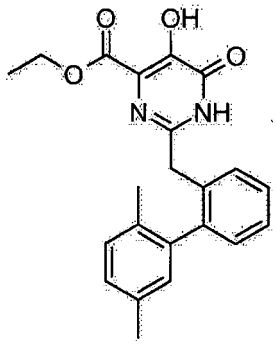


[0348] 利用与实施例33中相同的通用操作使用2,5-二甲基苯基硼酸(4.21g,28.1mmol,Eq:1.1)制备了该化合物。标题化合物以无色油状物的形式被制备(4.7g;83%)。

[0349] ^{1}H NMR(300MHz;$CDCl_3$) δ ppm 2.01(s,3H),2.35(s,3H),3.44(s,2H),6.96(s,1H),7.08-7.24(m,3H),7.34-7.47(m,2H),7.53-7.62(mm 1H).

[0350] 实施例39:2-(2',5'-二甲基-联苯-2-基甲基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸乙酯的制备

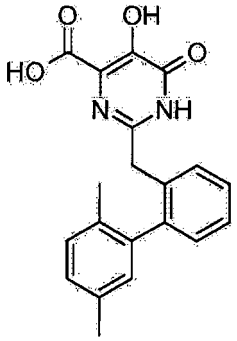
[0351]



[0352] 利用与实施例32中相同的通用操作使用2-(2',5'-二甲基联苯-2-基)乙腈(4.7g,21.2mmol)和丁-2-炔二酸二乙酯(3.61g,21.2mmol)制备了该化合物。分离标题产物,为白色固体(0.84g;10%)。LCMS:m/z = 379(MH+)。

[0353] 实施例40:2-(2',5'-二甲基-联苯-2-基甲基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸的制备

[0354]

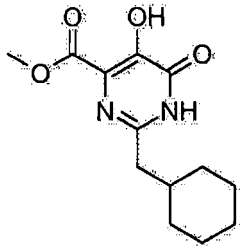


[0355] 利用与实施例29中相同的操作使用2-(2',5'-二甲基-联苯-2-基甲基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸乙酯(22mg,58.1μmol)制备了该化合物,得到标题化合物,为灰白色固体(0.018g;95%纯度,84%收率)。LCMS:m/z = 349(M-H).

[0356] 实施例41:2-环己基甲基-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸甲酯的制

备

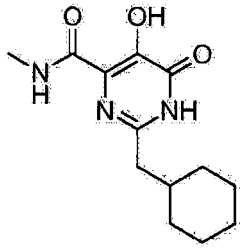
[0357]



[0358] 根据与实施例 32 中相同的操作使用 2- 环己基乙腈 (2.5g, 20.3mmol) 制备了该化合物。分离标题产物，为白色固体 (0.060g ;1%)。LCMS :m/z = 280(MH+).

[0359] 实施例 42 :2- 环己基甲基 -5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

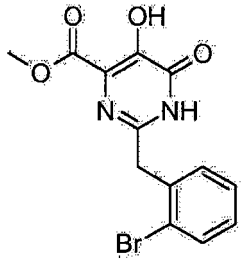
[0360]



[0361] 将 2-(环己基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (30mg, 113 μ mol)、甲胺 (2M 的 THF 溶液)(1.5ml, 3.00mmol) 和 MeOH(10ml) 的混合物在微波炉中于 140℃加热 40min。真空浓缩冷却的反应混合物。将残余物在 MeOH 和 Amberlyst 的混合物加热至全部产物溶解。通过过滤除去树脂，减压蒸发滤液至干，得到标题化合物，为灰白色固体 (0.011g ;35%，具有 95%纯度)。LCMS :m/z = 266(MH+).

[0362] 实施例 43 :2-(2- 溴 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

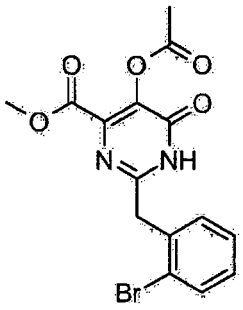
[0363]



[0364] 根据与实施例 18 中相同的操作使用 2-(2- 溴苯基) 乙腈 (0.50g ;2.5mmol) 和乙炔二甲酸二甲酯 (0.40g, 2.81mmol) 制备了该化合物。得到白色固体形式的标题产物 (0.084g ;9%)。LCMS :m/z = 340(MH+).

[0365] 实施例 44 :5- 乙酰氧基 -2-(2- 溴 - 苄基)-6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

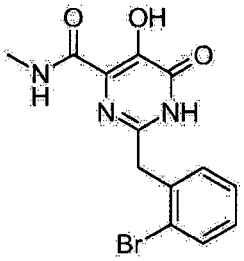
[0366]



[0367] 在圆底烧瓶中，将2-(2-溴苄基)-5,6-二羟基嘧啶-4-甲酸甲酯(300mg,885μmol)与DCM(10ml)合并，得到棕色混悬液。在室温缓慢地加入乙酰氯(1M的DCM溶液)(2.21ml,2.21mmol)。将该混合物搅拌1小时，然后倾倒在饱和NH_4Cl水溶液上，用DCM萃取。用盐水溶液洗涤有机相，干燥(Na_2SO_4)，减压蒸发至干。进行色谱处理(SiO_2;DCM)，得到标题产物，为白色固体(0.33g;97%)。LCMS:m/z = 381/383(MH+).

[0368] 实施例45:2-(2-溴-苄基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸甲基酰胺的制备

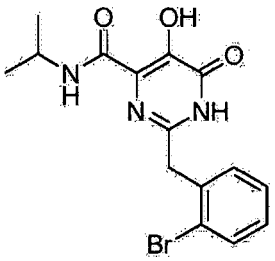
[0369]



[0370] 根据与实施例20中相同的操作使用2-(2-溴-苄基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸甲酯(0.08g;0.236mmol)制备了该化合物。得到白色固体形式的标题化合物(0.032g;40%)。LCMS:m/z = 339(MH+).

[0371] 实施例46:2-(2-溴-苄基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸异丙基酰胺的制备

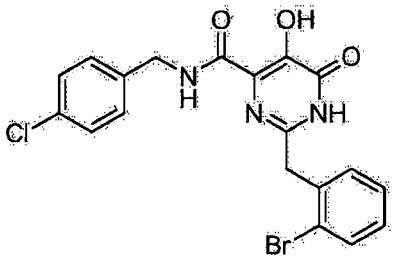
[0372]



[0373] 根据与实施例21中相同的操作使用2-(2-溴-苄基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸甲酯(0.08g;0.236mmol)和异丙基胺(0.4ml;4.7mmol)制备了该化合物。得到白色固体形式的标题化合物(0.021g;24%)。LCMS:m/z = 367(MH+).

[0374] 实施例47:2-(2-溴-苄基)-5-羟基-6-氧代-1,6-二氢-嘧啶-4-甲酸4-氯-苄基酰胺的制备

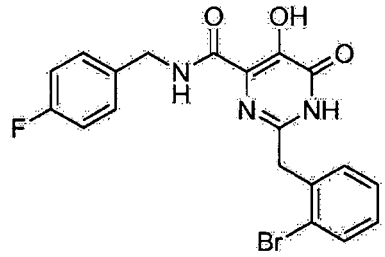
[0375]



[0376] 根据与实施例 21 中相同的操作使用 2-(2- 溴 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯 (0.08g ;0.236mmol) 和 4- 氯苄基胺 (0.5ml ;4.1mmol) 制备了该化合物。标题化合物以白色固体的形式被制备 (0.042g ;39%)。LCMS :m/z = 449(MH+).

[0377] 实施例 48 :2-(2- 溴 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸 4- 氟 - 苄基酰胺的制备

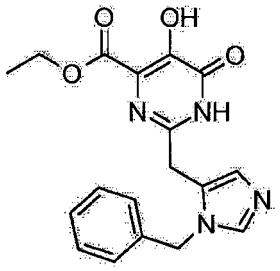
[0378]



[0379] 根据与实施例 21 中相同的操作使用 2-(2- 溴 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯 (0.08g ;0.236mmol) 和 4- 氟苄基胺 (0.5ml ;4.4mmol) 制备了该化合物。得到白色固体形式的标题化合物 (0.072g ;70%)。LCMS :m/z = 433(MH+).

[0380] 实施例 49 :2-(3- 苄基 -3H- 咪唑 -4- 基甲基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸乙酯的制备

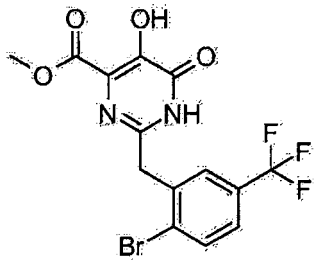
[0381]



[0382] 在 0℃将盐酸羟胺 (2.85g,41.1mmol) 在甲醇 (25ml) 中的溶液与氢氧化钾 (2.3g,41.1mmol) 在甲醇 (25ml) 中的溶液合并。通过过滤除去得到的盐,将滤液立即加入到 2-(1- 苄基 -1H- 咪唑 -5- 基) 乙腈 (1.62g,8.21mmol) 中。将得到的溶液在 60℃加热过夜,然后蒸发至干。将残余物用 $CHCl_3$(100ml) 吸收,加入丁 -2- 炔二酸二乙酯 (1.4g,8.21mmol)。将得到的混合物在 60℃加热过夜。冷却后,真空浓缩粗品反应混合物。用水和 EtOAc 处理残余物。分离有机相,用盐水洗涤,干燥 (Na_2SO_4),真空浓缩。将残余物在二甲苯 (2.5ml) 中于 140℃在微波炉中加热 40min。将冷却的混合物蒸发至干,溶于 MeOH,使其通过 Celite®,然后减压蒸发至干。通过制备型 HPLC 纯化,得到所需的产物,为黄色固体 (0.014g ;0.36%)。LCMS :m/z = 355(MH+)75%纯度。

[0383] 实施例 50 :2-(2- 溴 -5- 三氟甲基 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

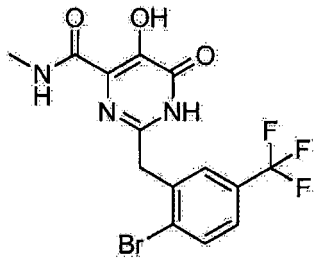
[0384]



[0385] 按照实施例 18 中所用的通用操作使用 2- 溴 -5-(三氟甲基) 苯基乙腈 (1g ; 3.78mmol) 和丁 -2- 炔二酸二甲酯 (1.09g, 7.67mmol) 进行制备,得到所需的产物,为灰白色固体 (0.29g ;16%)。LCMS :m/z = 408(MH+).

[0386] 实施例 51 :2-(2- 溴 -5- 三氟甲基 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

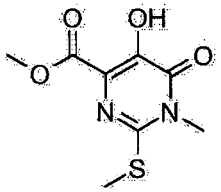
[0387]



[0388] 根据与实施例 21 中所述相同的操作使用 2-(2- 溴 -5- 三氟甲基 - 苄基)-5- 羟基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯 (0.080g ;0.197mmol) 和 2M 甲胺的 THF 溶液 (1ml) 制备了该化合物。得到灰白色固体形式的标题产物 (0.043g ;53%)。LCMS :m/z = 427(MH+).

[0389] 实施例 52 :5- 羟基 -1- 甲基 -2- 甲基硫基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

[0390]

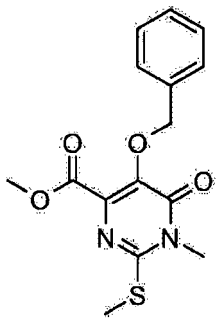


[0391] 在圆底烧瓶中,将氰硫基甲烷 (thiocyanatomethane)(17.5g, 239mmol) 和 N- 甲基羟胺盐酸盐 (20g, 239mmol) 与 EtOH(100ml) 合并,得到淡黄色溶液。在 RT 历经 8min 缓慢地加入碳酸钠 (12.7g, 120mmol) 在水 (50ml) 中的溶液。将得到的混合物在 RT 搅拌 2.5 天,然后用冰浴冷却。历经 10min 缓慢地加入丁 -2- 炔二酸二甲酯 (34.0g, 239mmol),将得到的混合物搅拌 2 小时,同时保持内部温度低于 22℃。加入冰水和 EtOAc。分离有机层,用盐水洗涤,用 Na_2SO_4 干燥,真空浓缩。将得到的 5-(2- 甲氧基 -2- 氧代乙基)-2- 甲基 -3-(甲基硫基)-2,5- 二氢 -1,2,4- 噁二唑 -5- 甲酸甲酯 (62.7g, 239mmol) 放入圆底烧瓶中,溶于

二甲苯 (110ml)，然后在 140℃加热 48 小时，冷却，然后蒸发至干，得到粗品标题产物，为棕色固体。LCMS :m/z = 231(MH+).

[0392] 实施例 53 :5- 苄基氧基 -1- 甲基 -2- 甲基硫基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

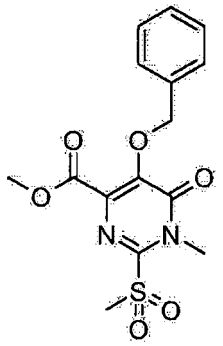
[0393]



[0394] 在圆底烧瓶中，将 5- 羟基 -1- 甲基 -2-(甲基硫基)-6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (55.0g,239mmol) 和碳酸钾 (33.0g,239mmol) 与 DMF(200ml) 合并，得到黑色混悬液。加入苄基溴 (40.9g,239mmol)，将得到的混合物在室温搅拌 3.5 天。通过添加冷水猝灭反应。过滤该混合物，得到棕色固体。进行色谱处理 (SiO_2;10% -50% EtOAc 的己烷溶液)，得到所需的产物，为灰白色固体 (14.3g ;18%)。LCMS :m/z = 321(MH+).

[0395] 实施例 54 :5- 苄基氧基 -2- 甲磺酰基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

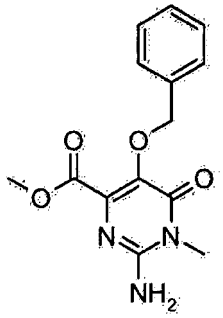
[0396]



[0397] 在 1L 的圆底烧瓶中，将 5-(苄基氧基)-1- 甲基 -2-(甲基硫基)-6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (5.57g,17.4mmol) 与 MeOH(400ml) 和 DCM(50ml) 合并。加入 oxone(21.4g,34.8mmol) 在水 (100ml) 中的溶液。将该混合物在室温搅拌 5 小时，然后蒸发至干。将残余物用 EtOAc 吸收，用 3N NaOH 水溶液、水和盐水洗涤，用 Na_2SO_4 干燥，减压浓缩，得到标题化合物，为白色固体 (3.7g ;60%)。LCMS :m/z = 353(MH+).

[0398] 实施例 55 :2- 氨基 -5- 苄基氧基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

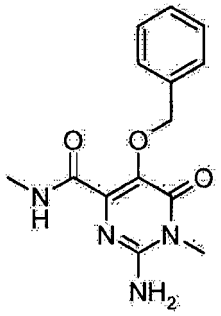
[0399]



[0400] 在圆底烧瓶中，将 5-（苄基氧基）-1- 甲基 -2-（甲基磺酰基）-6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (3.65g,10.4mmol) 与 CH_3CN(50ml) 合并，得到无色溶液。在 25℃使气态氨鼓泡 20min。通过闪式色谱法（硅胶，30% -50% EtOAc 的己烷溶液）、然后通过第二个柱 (5% MeOH/DCM) 纯化粗物质，得到标题产物，为白色固体。LCMS :m/z = 290(MH+).

[0401] 实施例 56 :2- 氨基 -5- 苄基氧基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

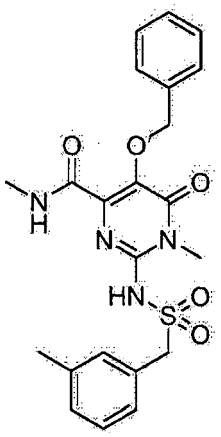
[0402]



[0403] 向 2- 氨基 -5-（苄基氧基）-1- 甲基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯 (0.907g,3.14mmol,Eq :1.00) 的混合物中加入甲胺的 2M 的 THF 溶液 (12ml,24.0mmol)。将该混合物在微波炉中于 140℃加热 2h。真空浓缩粗品反应混合物，得到标题产物，为灰白色固体 (0.90g ;100%)。LCMS :m/z = 289(MH+).

[0404] 实施例 57 :5- 苄基氧基 -1- 甲基 -6- 氧代 -2- 间 - 甲苯基甲磺酰基氨基 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

[0405]

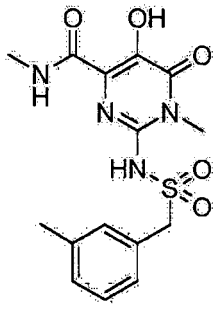


[0406] 将叔丁醇钾 (75.9mg,676 μmol) 加入到 2- 氨基 -5-（苄基氧基）-N,1- 二甲基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酰胺 (150mg,520 μmol) 在 THF(15.0ml) 和 DMF(3ml) 中

的溶液中。将得到的混合物搅拌 10min，然后用冰浴冷却。向该混合物中缓慢地加入 (3- 甲基苯基) 甲磺酰氯 (140mg, 684 μ mol) 在 THF(1ml) 中的溶液。将反应混合物在室温搅拌过夜。再加入 (3- 甲基苯基) 甲磺酰氯 (140mg, 684 μ mol) 在 THF(1ml) 中的溶液，然后将该混合物在室温搅拌 48 小时。用 EtOAc 稀释得到的混合物，用饱和 $NaHCO_3$ 水溶液和盐水洗涤。用 Na_2SO_4 干燥有机层，真空浓缩。进行闪式色谱法 (硅胶，0% -2% MeOH 的 DCM 溶液)，得到所需的产物，为淡黄色固体 (0.070g ;29%)。LCMS :m/z = 457(MH+).

[0407] 实施例 58 :5- 羟基 -1- 甲基 -6- 氧代 -2- 间 - 甲苯基甲磺酰基氨基 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酰胺的制备

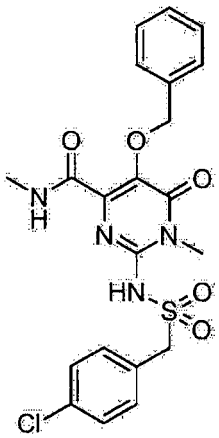
[0408]



[0409] 将 10% 披钯碳 (palladium on carbon)(20mg, 18.8 μ mol) 加入到含有 5-(苄基氧基)-N,1- 二甲基 -6- 氧代 -2-(间 - 甲苯基甲基磺酰氨基)-1,6- 二氢嘧啶 -4- 甲酰胺 (0.07g, 153 μ mol) 在乙酸乙酯 (5ml) 和 MeOH(5ml) 中的溶液的圆底烧瓶中。用氮气给得到的混合物脱气，抽真空，用氢气净化。将该混合物于室温在氢气气氛下搅拌 1 小时，过滤，减压蒸发至干。用己烷和 DCM 洗涤残余物，从 MeOH/Et_2O 中结晶，得到标题化合物，为灰白色固体 (0.03g ;53%)。LCMS m/z = 367(MH+).

[0410] 实施例 59 :5- 苄基氧基 -2-(4- 氯 - 苯基甲磺酰基氨基)-1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

[0411]

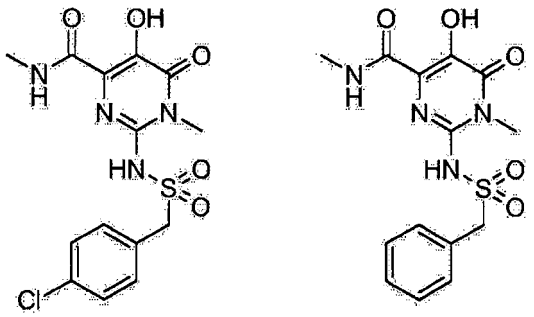


[0412] 在圆底烧瓶中，将 2- 氨基 -5-(苄基氧基)-N,1- 二甲基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酰胺 (250mg, 867 μ mol, Eq :1.00) 与 THF(20ml) 合并，得到白色混悬液。加入 DMF(4ml)，然后加入叔丁醇钾 (117mg, 1.04mmol, Eq :1.2)。将得到的混合物在室温搅拌 10min，然后用冰浴冷却。向其中缓慢地加入 (4- 氯苯基) 甲磺酰氯 (240mg, 1.07mmol, Eq : 1.23) 在 THF(1ml) 中的溶液。在室温搅拌 14h 后，再加入 t-BuOK(234mg)。将该混合物搅

拌 5min，用冰浴冷却，然后再加入（4- 氯苯基）甲磺酰氯（240mg，1.07mmol）。将反应混合物在 RT 搅拌 72 小时，然后用 EtOAc 稀释，用饱和 $NaHCO_3$ 水溶液和盐水洗涤。在 EtOAc 溶液中沉淀出一些固体，将其通过过滤收集。将剩余的滤液蒸发至干，通过闪式色谱法（硅胶，2%-6% MeOH 的 DCM 溶液）纯化，然后用 EtOAc/Hex 研磨。合并固体，得到所需的产物，为白色固体（0.210g；51%）。LCMS m/z = 477(MH+).

[0413] 实施例 60：2-(4- 氯 - 苯基甲磺酰基氨基)-5- 羟基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺和 5- 羟基 -1- 甲基 -6- 氧代 -2- 苯基甲磺酰基氨基 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

[0414]



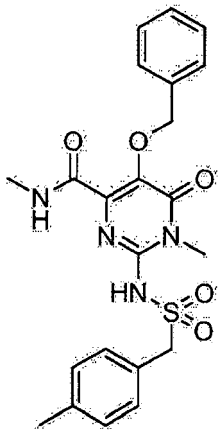
[0415] 在圆底烧瓶中，将 5-（苄基氧基）-2-((4- 氯苯基）甲基磺酰氨基)-N,1- 二甲基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酰胺（0.16g，335μmol）与乙酸乙酯（40ml）和 MeOH(40.0ml) 合并，得到白色混悬液。加入 5% 披钯碳（50mg，470μmol），用氮气给该溶液脱气。将该混合物于室温在氢气气氛（气囊）下搅拌 1 小时，然后通过过滤除去催化剂，将滤液蒸发至干。通过制备型 HPLC 纯化，得到：

[0416] 2-(4- 氯 - 苯基甲磺酰基氨基)-5- 羟基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺，为白色无定形固体（0.026g；20%）。LCMS：m/z = 387(MH+).

[0417] 5- 羟基 -1- 甲基 -6- 氧代 -2- 苯基甲磺酰基氨基 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺，为白色无定形固体（0.022g；17%）。LCMS：m/z = 353(MH+).

[0418] 实施例 61：5- 苄基氧基 -1- 甲基 -6- 氧代 -2- 对 - 甲苯基甲磺酰基氨基 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

[0419]

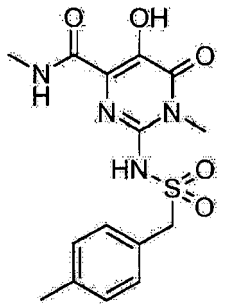


[0420] 将叔丁醇钾（93.8mg，836μmol）加入到 2- 氨基 -5-（苄基氧基)-N,1- 二甲基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酰胺（110mg，380μmol）在 THF(10ml) 在 DMF(2ml) 中的

溶液中［注解：请检查］。10min 后，用冰浴冷却反应混合物，然后加入（4- 甲基苯基）甲磺酰氯（93.7mg，458μmol）在 THF（2ml）中的溶液。70min 后，加入 EtOAc 和 1N NaOH 水溶液。用 EtOAc、然后用 DCM 萃取有机相。用水和盐水洗涤合并的有机相，用 Na_2SO_4 干燥，蒸发至干。进行色谱处理（硅胶，0-2% MeOH 的 DCM 溶液），得到标题化合物，为浅黄色固体（0.080g；46%）。LCMS：m/z = 457（MH+）.

[0421] 实施例 62：5- 羟基 -1- 甲基 -6- 氧代 -2- 对 - 甲苯基甲磺酰基氨基 -1,6- 二氢 - 嘧啶 -4- 甲酸甲基酰胺的制备

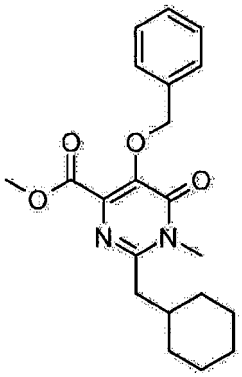
[0422]



[0423] 将 5-（苄基氧基）-N,1- 二甲基 -6- 氧代 -2-（对 - 甲苯基甲基磺酰氨基）-1,6- 二氢嘧啶 -4- 甲酰胺（80mg，175μmol）、披钯碳（186mg，87.6μmol）、MeOH（5ml）和乙酸乙酯（5ml）的混合物置于氢气气氛下。搅拌 1.5 小时后，过滤反应混合物，蒸发至干。从 MeOH 中结晶，得到标题产物，为灰白色固体（0.045g；70%）。LCMS：m/z = 367（MH+）.

[0424] 实施例 63：5- 苄基氧基 -2- 环己基甲基 -1- 甲基 -6- 氧代 -1,6- 二氢嘧啶 -4- 甲酸甲酯的制备

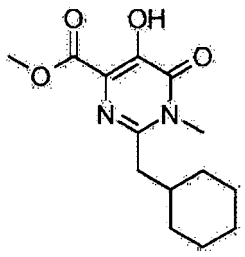
[0425]



[0426] 将溴化环己基甲基镁溶液（1.77ml；885μM 的 0.5M 的 THF 溶液）滴加到 5- 苄基氧基 -2- 甲磺酰基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯（0.26g；738μM）在 THF（10ml）中的溶液中。在室温搅拌 1h 后，通过添加饱和氯化铵溶液猝灭反应混合物。将产物萃取入 EtOAc 中，用盐水洗涤，干燥（Na_2SO_4），减压蒸发至干，得到标题产物，为无色油状物（0.040g；70%）。LCMS：m/z = 367（MH+）.

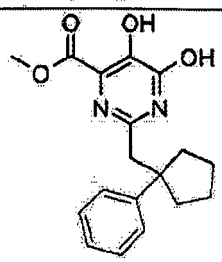
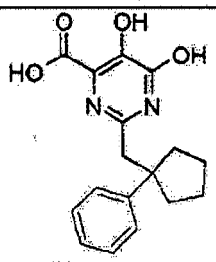
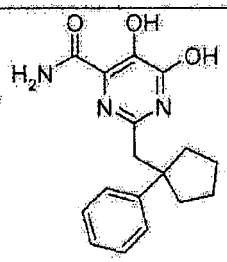
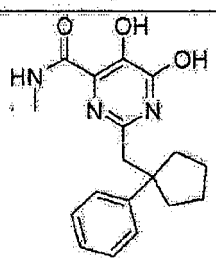
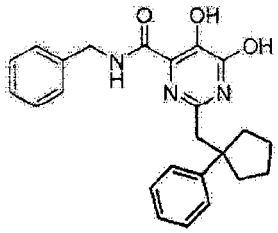
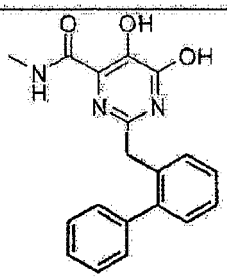
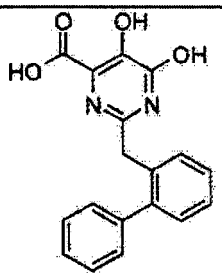
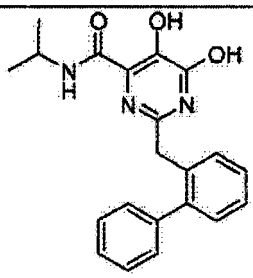
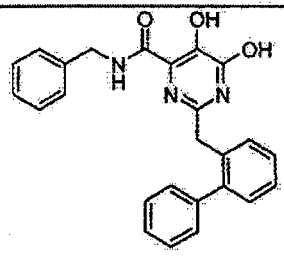
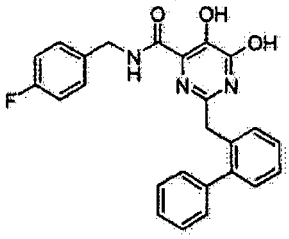
[0427] 实施例 64：2- 环己基甲基 -5- 羟基 -1- 甲基 -6- 氧代 -1,6- 二氢 - 嘧啶 -4- 甲酸甲酯的制备

[0428]

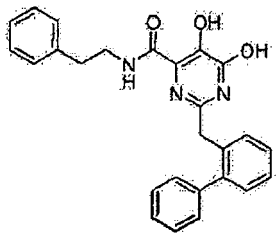
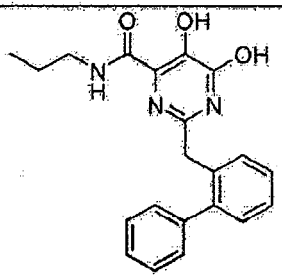
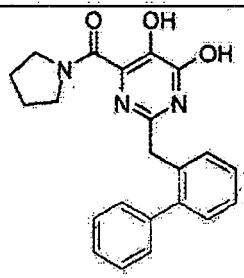
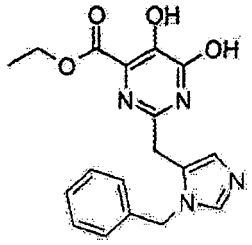
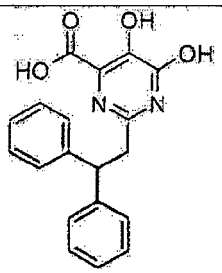
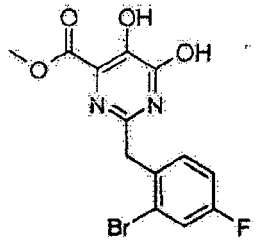
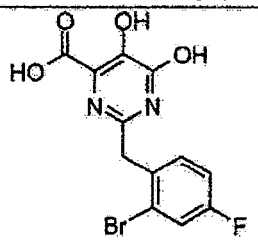
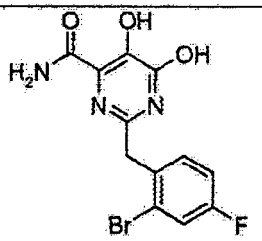
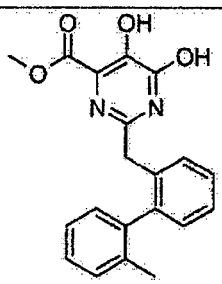
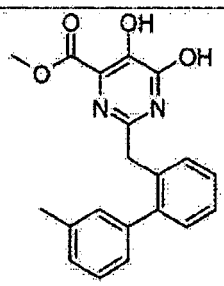


[0429] 将5-(苄基氧基)-2-(环己基甲基)-1-甲基-6-氧代-1,6-二氢嘧啶-4-甲酸甲酯(60mg,162μmol)和20%披氢氧化钯碳(palladium hydroxide on carbon)(11.4mg,16.2μmol)在EtOAc(10ml)中的混合物置于氢气气氛下,在室温搅拌过夜。过滤该混合物,然后蒸发至干。进行色谱处理(SiO_2;0-20%EtOAc的己烷溶液),得到标题产物,为白色固体(0.032g;70%)。LCMS:m/z = 281(MH+).

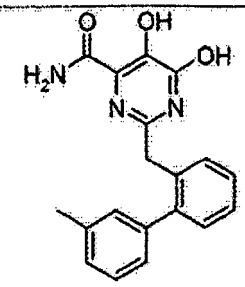
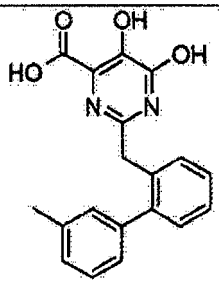
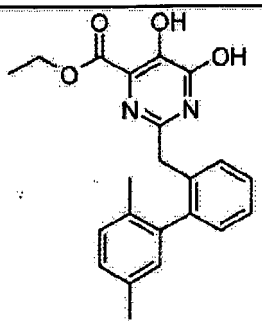
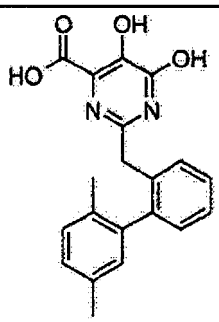
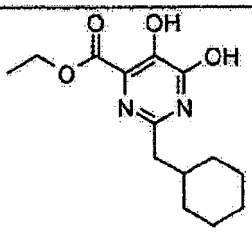
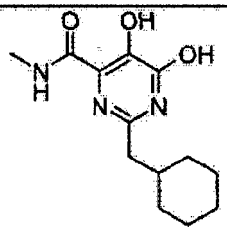
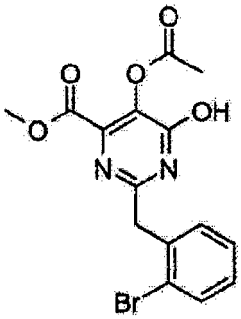
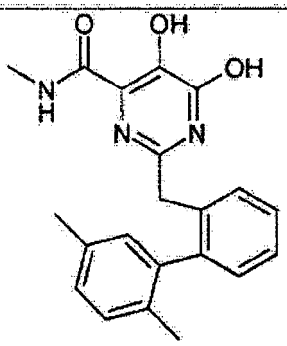
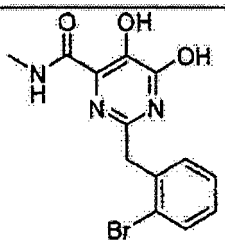
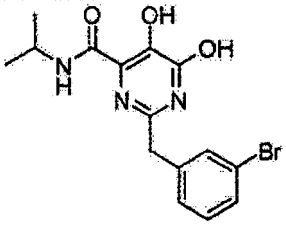
[0430]

结构	FRET	CPE	结构	FRET	CPE
	IC_{50} = 0.41 μM	IC_{50} = 12 μM		IC_{50} = 0.08 μM	IC_{50} = 49 μM
	IC_{50} = 0.24 μM	IC_{50} = 42 μM		IC_{50} = 0.14 μM	IC_{50} = 22 μM
	IC_{50} = 1.1 μM	无活性		IC_{50} = 0.66 μM	无活性
	IC_{50} = 0.04 μM	无活性		IC_{50} = 8.2 μM	IC_{50} = 23 μM
	IC_{50} = 16 μM	无活性		IC_{50} = 1.7 μM	IC_{50} = 10 μM

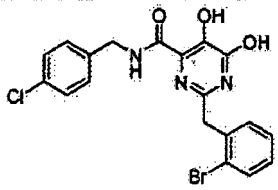
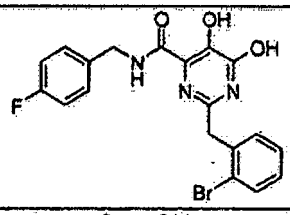
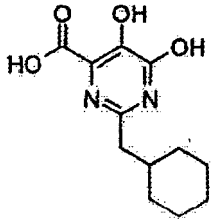
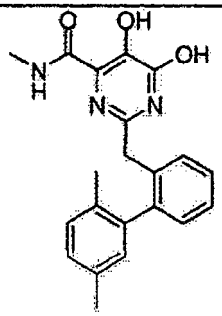
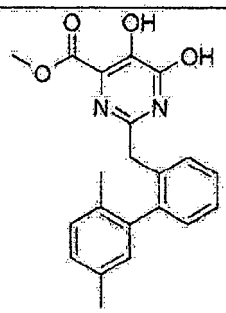
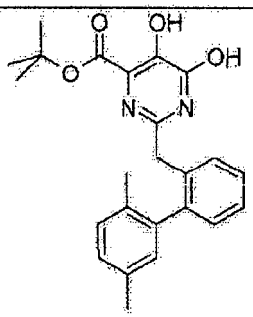
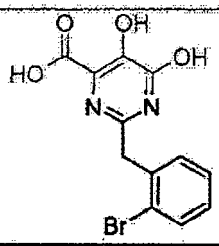
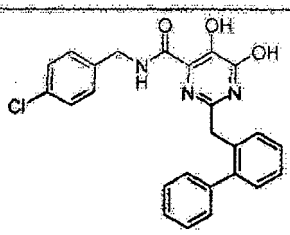
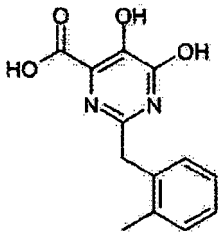
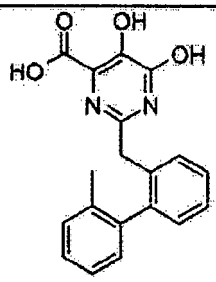
[0431]

	IC_{50} = 3.8 μM	IC_{50} = 8 μM		IC_{50} = 8.8 μM	not determ.
	IC_{50} = 1.1 μM	IC_{50} = 89 μM		IC_{50} = 9.5 μM	无活性
	IC_{50} = 2.5 μM	无活性		IC_{50} = 1.5 μM	无活性
	IC_{50} = 0.18 μM	无活性		IC_{50} = 2.7 μM	无活性
	IC_{50} = 0.12 μM	无活性		IC_{50} = 0.35 μM	not determ.

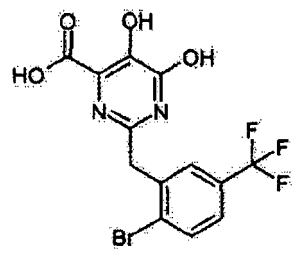
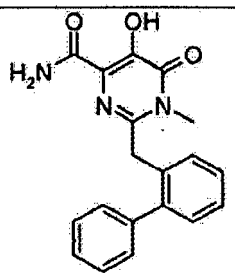
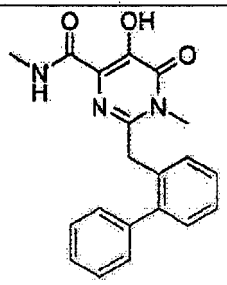
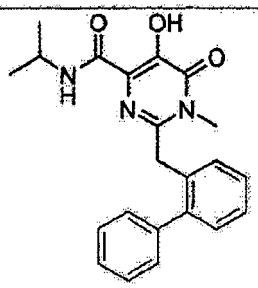
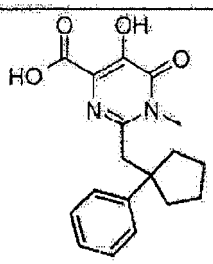
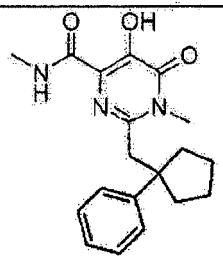
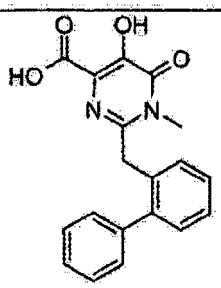
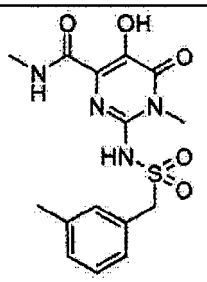
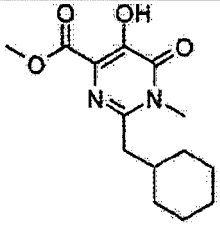
[0432]

	IC_{50} = 0.55 μM	not determ.		IC_{50} = 0.23 μM	无活性
	IC_{50} = 0.22 μM	IC_{50} = 9.1 μM		IC_{50} = 0.03 μM	无活性
	IC_{50} = 3.2 μM	无活性		IC_{50} = 6.5 μM	无活性
	IC_{50} = 7.9 μM	无活性		IC_{50} = 0.53 μM	无活性
	IC_{50} = 5.7 μM	无活性		IC_{50} = 23 μM	not determ.

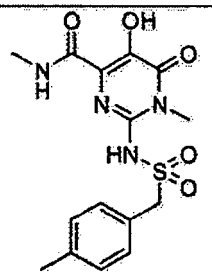
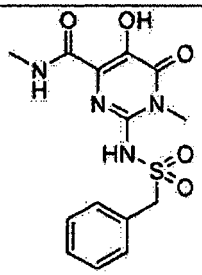
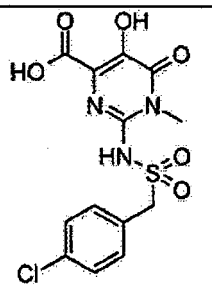
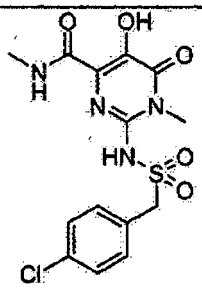
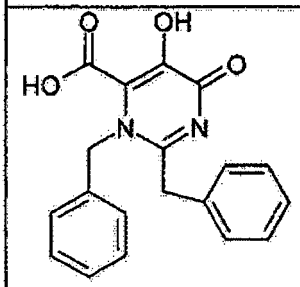
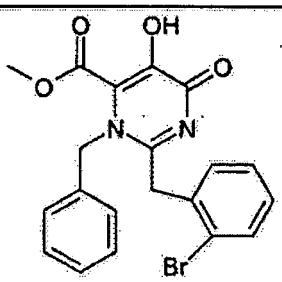
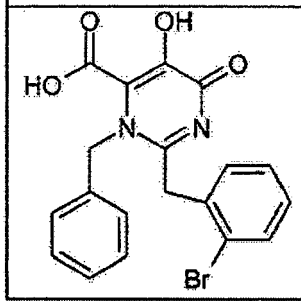
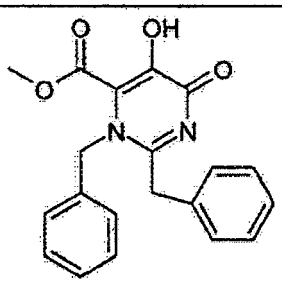
[0433]

	37% @ 10 μM	无活性		IC_{50} = 27 μM	无活性
	IC_{50} = 0.21 μM	无活性		IC_{50} = 0.53 μM	无活性
	IC_{50} = 0.15 μM	IC_{50} = 16 μM		IC_{50} = 1.1 μM	IC_{50} = 11 μM
	IC_{50} = 0.25 μM	无活性		IC_{50} = 1.8 μM	无活性
	IC_{50} = 0.27 μM	无活性		IC_{50} = 0.24 μM	无活性

[0434]

	IC_{50} = 0.16 μM	无活性		IC_{50} = 1.3 μM	无活性
	IC_{50} = 23 μM	无活性		IC_{50} = 14 μM	无活性
	IC_{50} = 0.26 μM	无活性		IC_{50} = 0.41 μM	IC_{50} = 11 μM
	IC_{50} = 1.3 μM	无活性		IC_{50} = 6.8 μM	无活性
				25% @ 10 μM	无活性

[0435]

	IC_{50} = 13 μM	无活性		IC_{50} = 3 μM	无活性
	IC_{50} = 0.54 μM	无活性		IC_{50} = 5.8 μM	无活性
	IC_{50} = 3.8 μM	无活性		23% @ 10 μM	IC_{50} = 34 μM
	IC_{50} = 5.7 μM	无活性		IC_{50} = 19 μM	无活性

[0436] not determ. =未测定

Abstract

The present invention relates to a compound having the general formula (Di), (Dii), or (Diii), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, formula (Di), (Dii), (Diii) which are useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.